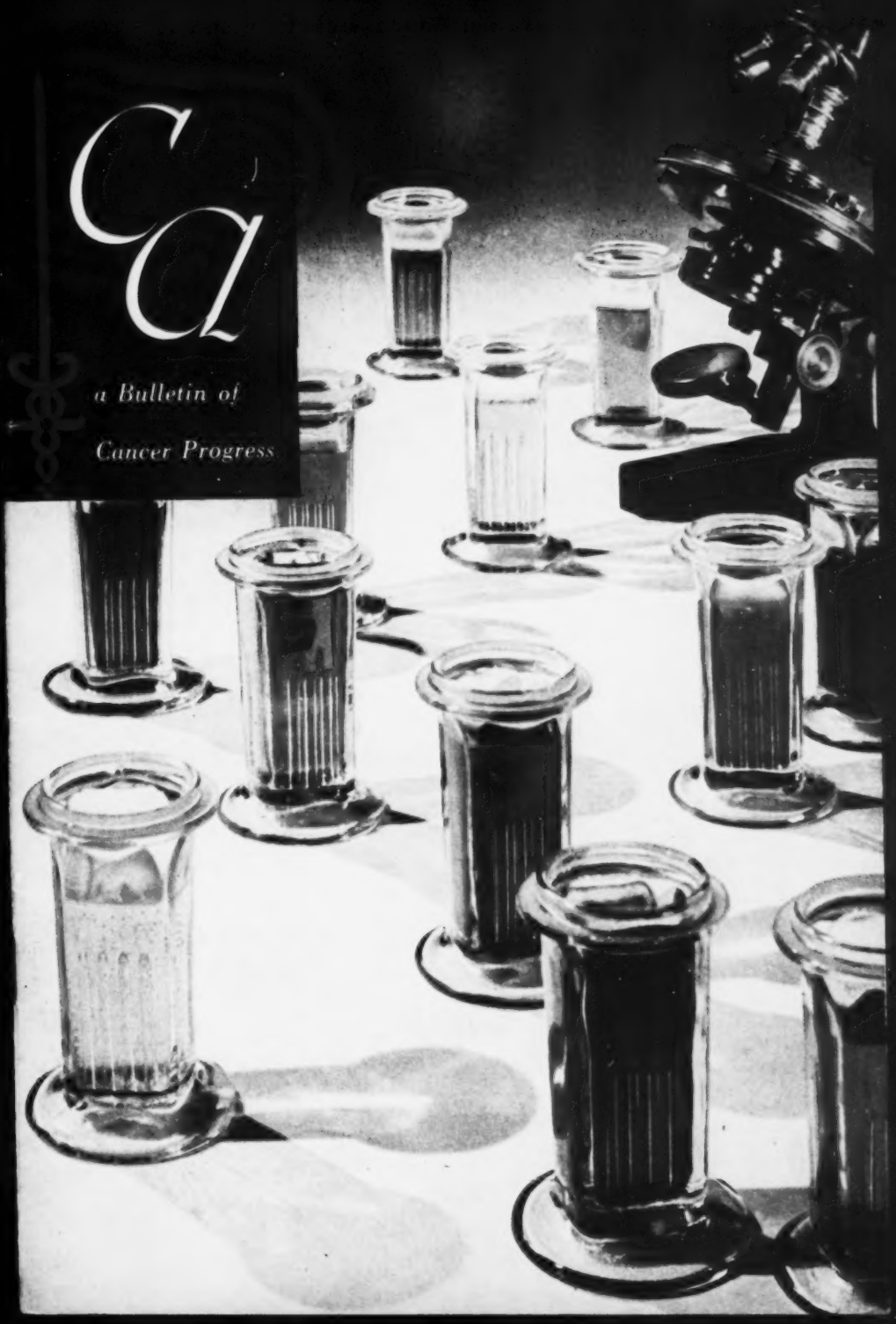
Ca

a Bulletin of

Cancer Progress



not one but four out of five

During the past decade the American Cancer Society has taken the initiative in the promotion of exfoliative cytology as an important adjunct in the diagnosis of early cancer of the uterus, particularly of the cervix. Extension of the use of this procedure has now led to its wide acceptance; so wide, indeed, that the supply of specially trained cytologists and technicians has fallen behind the demand for these examinations. The Society and its Divisions support a program for correcting this personnel deficiency through fellowships to pathologists for study of exfoliative cytology and scholarships to technicians for training in cytological screening.

Education in cytology sponsored by the Society includes national and international conferences, support of the Inter-Society Cytology Council, motion-picture films, and special articles in this journal, in *Cancer*, and in many lay magazines.

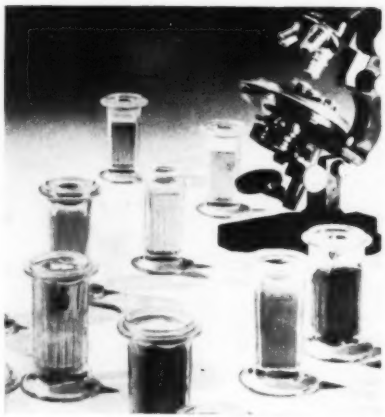
Substantial sums are provided for cytological research in many institutions.

It is recommended that the cell examination for uterine cancer be made a part of the annual periodic health examinations of all adult women, especially those more than thirty-five years of age. The medical profession is rapidly making provisions for the increasing volume of these examinations. The American Cancer Society is making every effort to meet the need for trained personnel. In this way cytology will contribute toward the salvage of a possible four instead of the present one out of five patients with cervical carcinoma.

David A. Wood, M.D.
President, American Cancer Society

Cover—

Symbolic representation of the contributions of Dr. George N. Papanicolaou to the development of the science of exfoliative cytology. The microscope shown was his silent companion when he first saw cancer cells in a smear of the uterine cervix almost forty years ago, during the time he was studying the normal cytology of the female rodent and human sex cycles —investigations upon which are based today's applications of his staining techniques and cytologic interpretation to the diagnosis of cancer of the cervix and other sites. The Coplin jars containing polychrome stains represent his substitution of alcoholic for the older aqueous staining solutions, resulting in more translucent coloration of cells and greater diagnostic accuracy—a decisive factor in the wide acceptance of the cytologic techniques of the Master Cytologist.



NEWSLETTER

JULY, 1957

Conference on Comparative Clinical and Biological Effects of Alkylating Agents, New York City, March 28-30, (Continued from May issue)

Stacey et al. (Chester Beatty): Esterification of the carboxyl group is the predominant reaction of some agents acting on the protein of serum albumin. The primary phosphate group is by far the most reactive center in DNA. In dilute solutions, bifunctional reagents crosslink within the same macromolecule of synthetic polymers, proteins, and DNA; at higher concentrations, they crosslink different molecules and may gel them. Internal crosslinking increases DNA coiling and reduces viscosity.

Auerbach (Edinburgh): Mutagens may act by a variety of mechanisms. Alkylating agents don't act by crosslinkage and probably not by -SH reactions.

Murphy (Sloan-Kettering Institute): Several alkylating agents were teratogenic and toxic to the twelve-day rat embryo and four-day chick embryo, and damaging to Sarcoma 180 explanted to chick-egg yolk sacs.

Sternberg (Sloan-Kettering Institute): Supralethal doses of alkylating agents act on the animal nervous system and may bring convulsions, paralysis, and death within twenty-four hours. Median lethal doses bring anorexia, vomiting, diarrhea, dehydration, leukopenia, and death in three to seven days.

Karnofsky (Sloan-Kettering Institute): Nausea and vomiting usually follow each injection of HN2, and bone-marrow depression is the major toxic effect most severely reflected in peripheral blood two to three weeks following treatment. There is no evidence that HN2 cures cancer. It is used principally when a prompt and maximal course of treatment is indicated--often in Hodgkin's disease, lympho-

sarcoma, carcinomas of the lung, ovary, and breast, and where there are cerebral or pulmonary metastases.

Israels et al. (University of Manitoba): Chlorambucil gave excellent remissions in three of thirty-five Hodgkin's cases (and some benefit in twenty-one), nine of twelve giant follicular lymphomas, twelve of twenty-seven chronic lymphocytic leukemias, and seven of twenty lymphocytic lymphomas. The drug was well tolerated. It is a valuable agent in the treatment of these diseases.

Rundles et al. (Duke University): TEM has been a most effective agent in lymphocytic leukemia and a valuable supplement to local radiation in malignant lymphomas and Hodgkin's, and very good in chronic granulocytic leukemia and polycythemia vera. About 50 per cent with widespread ovarian carcinomas and a few with undifferentiated metastatic carcinoma are benefited. The safe and effective oral dose varies considerably from patient to patient. Patients have taken the chemical more or less continuously for periods up to five years without toxic effect. We have found no real difference in antitumor selectivity between TEM and chlorambucil (CB 1348) when TEM dosage is adjusted.

Wright (New York University-Bellevue): Thio-TEPA induced a favorable response in 29 per cent, equivocal response in 11 per cent, and no response in 59 per cent of ninety-three cases of sarcomas, carcinomas, and miscellaneous tumors.

Galton (Chester Beatty): Myleran has been used continuously for from eight to forty-five months on twenty-five cases of chronic granulocytic leukemia and a median time of thirty-six months on thirty-four now-dead patients. It was successful in three chronic lymphatic leukemias and ineffective in twenty other cases of cancer.

Walpole (Manchester, England): Carcinogenic activity is not restricted to polyfunctional compounds--certain monofunctional ethyleneimine derivatives, without tumor-inhibiting activity, produce tumors. These observations have implications in environmental carcinogenesis.

Diamond (Memorial, N. Y.): In several particular clinical situations, HN2 and/or TEM are indispensable for the adequate and safe management of malignant lymphomas and leukemias. The radiomimetic effects are valuable in patients with involved neurological syndromes, vena caval compression, and acute, toxic, highly febrile syndrome.

(Continued after page 144)

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Please address all correspondence to
WILLIAM H. STONER, M.D.
Executive Editor
American Cancer Society, Inc.
521 West 57 St., New York 19, N. Y.

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Keeping up

The Cause of Cancer

The *Journal of the National Cancer Institute* invites thoughtful speculative papers presenting hypotheses on neoplastic disease, its nature, origin, and development. This is the first of such a series and presents the hypothesis, with some supporting evidence, that the leukemias, lymphomas, and cancers may have a common etiology. According to this concept, which can unify many of the current concepts, malignancy is due not to the presence of something but to the absence of something, probably of one or more enzyme systems—any enzyme system necessary for a normal life span of the differentiating cell. If this unifying concept is correct, the only real control of cancer would come from finding a replacement for the missing enzyme systems. Search should be made, in the normal rather than in the cancer cell, for growth inhibitors. They should be characterized chemically and synthesized. Administration of B_{12} leads to restoration of the normal life span of the cell. Similarly discovery and replacement of the missing factor for a particular malignant tumor in a particular individual could result in restoration of normal rate of cell growth and normal life span of the cell. Chemically mature differentiating cells produce inhibitors of cell division. Lack of these inhibitors permits the emergence of the capacity for unlimited cell division and uncontrolled growth that is possessed by unicellular organisms and by the early dividing cell of every fundamental cell type in at least some stage of postnatal life. Current theories of the etiology of malignancy are not displaced by this hypothesis, but rather unified, in that they have in common the fact that they predispose to the development of some change in the cell that leads to a shortened life span and hence to the lack of growth inhibitors. The concept presented here does not simplify the cancer problem, but does unify the many facts now known.

Osgood, E. E.: A unifying concept of the etiology of the leukemias, lymphomas, and cancers. J. Nat. Cancer Inst. 18:155-166, Feb., 1957.

Adrenalectomy in Breast Cancer

A critical analysis was made of the results of adrenalectomy for metastatic carcinoma of the breast in fifty-eight women at the Steroid Tumor Clinic of the University of Illinois and the Presbyterian Hospital between February, 1952, and August, 1955. Of this group, eight died in the immediate postoperative period, worthwhile palliation was obtained in thirteen, three more demonstrated objective regression, and thirty-four were not improved. The methods of patient selection for treatment by adrenalectomy is still unsatisfactory, and it is still impossible to predict what patients are likely to respond to the procedure. There is no clinical or laboratory criterion that can be used as a standard in assessing tumor regression or progression. There was no correlation between previous response to various therapies and the results of adrenalectomy. Great difficulty was encountered in the evaluation of objective regressions and improvement in symptoms. Improvements based on bone pain, changes in activity of serum alkaline phosphatase, chart films, and even on dramatic gross shrinkage of soft-tissue metastases and lymph nodes are often illusory and do not always indicate real clinical progress. The authors raise many

with Cancer

doubts as to the actual efficacy and real worth of this formidable procedure that produces worthwhile palliation in only about 25 per cent of cases. Evaluation of a large pooled series is necessary before the validity of adrenalectomy for metastatic breast carcinoma can be established.

Perlia, C. P.; Kofman, S.; Nagamani, D., and Taylor, S. G., III: Critical analysis of palliation produced by adrenalectomy in metastatic cancer of the female breast. Ann. Int. Med. 45: 989-1000, Dec., 1956.

Biological Approach to Cancer

Cancer research is heavily biased, particularly in America, toward the elaboration of tests for early diagnosis and toward its cure by nonsurgical means. The essential phenomenon in cancer is growth of cells free from the normal control. Cancer is not due to weakness of the organism but to a change in the character of the cells rendering them insusceptible to the normal control. The change is a genetic one and it is immaterial whether investigation will eventually give a more precise label to the genetic change, whether it represents a true somatic mutation, transfer of plasmagenes, incorporation of a virus into a "provirus" state, or some new, yet unformulated, concept. Any general basis for neoplastic growth must be related directly to the function of control and any other type of associated change must be regarded as secondary. Therefore it is impossible to accept Warburg's hypothesis that a change from aerobic to anaerobic glycolysis is the essential feature of cancer cells. If cancer is a negative biological phenomenon like starvation, scurvy, agammaglobulinemia, or phenylpyruvic oligophrenia, the only way to discuss its relation to general biology is to use the phenomena of cancer as seen clinically and experimentally to throw light on the nature of normal controls in the organism. In the mammalian body the widely varied differentiated cells differ greatly in the way they are produced, in their potentiality for multiplication, and in their average life span. Cells of epithelial surfaces of tissues exposed to external or internal environments—skin, and alimentary and respiratory mucous membranes —are always growing and it is significant that the incidence of cancer in these situations is high. Organs whose linings are modified sharply in relation to sexual periodicities of menstruation, pregnancy, and lactation are rather closely related to the skin surfaces and are subject to frequent incidence of cancer. The hormonal control of growth is applied effectively in chemotherapy, as in the use of estrogens in prostatic carcinoma. Changing hormone concentrations can trigger biologically appropriate changes in various target organs and tissues. Probably all cells are potentially subject to hormonal control. The pituitary control of thyroid function provides one of the most clearly manifested feed-back mechanisms in biological control. Thiouracil and other goitrogenic substances which decrease thyroxin output induce formation of thyroid tumors as a result of stimulation by pituitary thyrotropic hormone. A significant proportion of the control of cellular relations is intrinsic to the cells themselves. The first requirement for malignant growth is a loss of the control mediated by physiological contact with adjacent cells. Proliferative reactions must be seen against the background of normal controls, a specially important type being the proliferative response to certain virus infections. It has been shown that the labile

non-cellular antigen can be extracted from nuclei which will provoke homograft immunity and it is probable that this antigen, a DNA-protein complex, is concerned in provoking immunological tolerance. The difference between a mutation occurring in a germ cell and one occurring in a somatic cell depends on the extent and distribution of the cells descendant from that in which the mutation occurred. Modification of one cell or of any small proportion of the order characteristic of mutation will have no detectable effect on the function of the tissue unless one condition is fulfilled, that is that the mutation results in a differential survival advantage for descendants of the mutant cell over that of descendants of normal cells. Somatic mutation in higher animals is of no significance unless the cell loses some part of its normal control of its capacity to reproduce. The only mutations of significance are those along the road toward cancer and they are almost the only ones detectable even in principle. Change from normal cell to cancer cell is not by a single step. There is first the clinical evidence of precancerous changes in organs like breast, prostate, or skin. Recurrences are more malignant than the tumor removed and tumors held in check by hormone therapy or irradiation always eventually break away from control. With increasing age more and more patches of cells in expendable tissues are the offspring of cells which have undergone more than one mutation in the line of progression to cancer. This is illustrated by the skin on the back of the hand of an elderly man from its mosaic of color and texture. Cowdry regards these changes as mutational in origin. The claim that all cancers are of infective character is absurd in the present state of knowledge. The oncolytic action of certain viruses raises the hope that eventually we may see therapeutic use of viruses which, while lethal for tumors, have no action on normal tissues. That pure cell lines maintained in tissue culture can become malignant is one of the most decisive arguments against a necessary part being played by viruses in carcinogenesis. Cancer viruses represent simply one rather potent means by which what is functionally equivalent to somatic mutation can be produced. Probably all viruses have some capacity to provoke proliferation but the commonly versed claim that all proliferative processes are due to viruses is untenable. One of the most encouraging developments in medicine has been the recognition that a very large proportion of lung cancer and of other environmental cancer has a definite etiology and therefore is theoretically preventable. Cigarette smoke, diesel exhaust, and excessive radiation are to be avoided. It is impossible to say that any dose of radiation is harmless. In diagnosis the application of fluorescent antibody-studies to exfoliated cells might prove useful. There is little ground for optimism about cancer. Everything suggests that the impact of environment must inexorably lead to accumulations of mutant cells, some of which will have malignant descendants if life persists long enough. The two types of environmental stimuli—hydrocarbons and ionizing radiation—are increasing in importance. It is difficult to envisage effective means of preventing cancer. In preventive management of cancer we must be prepared not only for failure but for sharp increase in the incidence of cancer with further elaboration of modern technology. In the meantime we must adopt the orthodox maxim, "Recognize the cancerous lesion as early as possible and excise it."

Burnet, Sir M.: Cancer—A biological approach. I. The processes of control. II. The significance of somatic mutation. Brit. M. J. 1:779-786, April 6, 1957; III. Viruses associated with neoplastic conditions. IV. Practical applications. 841-847, April 13, 1957.

Cervical Carcinoma in Situ

What is now referred to as carcinoma in situ of the uterine cervix has been known for many years as early carcinoma. In an attempt to detect and to cure very early carcinomas, attention has been focused on carcinoma in situ, and the widespread acceptance and use of vaginal and cervical smears have stimulated this interest. Carcinoma in situ shows all the criteria of malignancy except invasion.

The changes are entirely intraepithelial and are sharply limited. All efforts should be directed toward recognition of a malignant tumor before it starts to invade. Patients with carcinoma in situ are on an average ten years younger than those with invasive cancer. That carcinoma in situ and invasive carcinoma of the cervix are related is shown by the fact that both are found much less frequently in Jewish women. Of seventy-five lesions at first interpreted as carcinoma in situ, fifty-five were later discovered to be invasive when more tissue was available. Experimental carcinoma from application of carcinogens goes through a stage resembling carcinoma in situ in every respect, but the lesion goes on to invasion and sometimes to metastasis without a silent interval. It has never been proved that some cancers start as noninvasive lesions. It is more probable that even early cancer cells multiply without regard to the neighboring structure and are thus immediately invasive. It is possible that, in carcinoma in situ, the apparent active growth, huge mitotic figures, and anaplasia are not present in growing cells, but are caused by a sudden arrest in the ability to continue in growth. The nature of carcinoma in situ is not understood, and there is reasonable doubt that it will invariably become invasive. When this appears to happen it is possible that the lesion was originally misdiagnosed, or that later coincidental and unrelated invasive cancer developed. Close follow-up of many untreated patients with such lesions is essential to learn more about carcinoma in situ.

Saphir, O.: Carcinoma in situ of the cervix: early true carcinoma or a noninvasive lesion? [Editorial.] Obst. & Gynec. 9:368-370, March, 1957.

Latent Prostatic Cancer

Latent cancer is found unsuspected and symptomless in the skin, uterine cervix, lung, kidney, thyroid, stomach, and prostate. The cytological characters of malignancy may remain latent for years. Some cases may develop into active carcinoma and others may regress. Benign hypertrophy of the prostate usually commences in the internal group of gland, and carcinoma in the outer group. Carcinoma of the prostate may invade the capsule, lymphatics, and blood vessels while still very small. Prostate glands removed at necropsy from patients who have died of some other disease are commonly found to contain histological carcinomas. At least 30 per cent of all men more than 50 years old have these lesions. These latent or retarded cancers grow very slowly, may infiltrate blood vessels and lymphatics, but seldom metastasize to distant sites. Beyond the age of 80 clinical cases of carcinoma of the prostate become less frequent and latent cases more common. A large proportion of the clinical cases in men more than 80 have no metastases. The cause of latency of tumors in man is unknown, but in some cases may be hormonal and possibly associated with ageing. There is no reliable method of distinguishing latent from active carcinomas. Histological examination cannot reveal the biological host resistance. Some cases diagnosed as clinical cancer may be of biologically latent type—those discovered accidentally after subtotal prostatectomy for benign hypertrophy, and those early cases detected by intensive investigation. Survival of such cases is long even without treatment.

Franks, L. M.: Latency and progression in tumours; the natural history of prostatic cancer. Lancet 2: 1037-1039, Nov. 17, 1956.

Cervical Cancer—Survival

During a twelve-year period, 552 cases of cervical carcinoma were seen at the Aberdeen (Scotland) Royal Infirmary. The standard method of treatment was the application of radium—50 mg. into the uterus and 37.5 mg. into each lateral vaginal fornix for twenty-four hours, three treatments being given at intervals of one and two weeks. Later about two out of nine patients were operated upon. There is no convincing evidence that surgery applied empirically can achieve better results than radiotherapy in equivalent cases. Operation is probably practical. The annual number of cases of cervical car-

cinoma seeking treatment is increasing. The falling death rate from cancer of the uterus shown in official reports may be due more to the fact that many more cases are receiving treatment than to improved methods of treatment. Since radiotherapy can be applied to a high proportion of cases, advances in irradiation techniques offer the best hope of improvement. It was estimated that the 552 cases referred to the hospital represented about 75 per cent of all cases in the Region. During the period 1942 to 1947 inclusive, five-year–survival rates were: Stage I, 54.8 per cent; Stage II, 29.5; Stage III, 16.9; and Stage IV, 0. Survival statistics from individual hospitals are of limited value. The death rate from cervical cancer is related to overcrowding, social-class distribution, and the predominant industry of an area, the highest rates being found in textile towns and seaports.

Lawson, J. G.: Cancer of the uterine cervix: some factors influencing survival rates. J. Obst. & Gynaec. Brit. Emp. 63:819-825, Dec., 1956.

Carcinoma of the Breast

A remarkable range of helpful measures is now available to the woman with cancer of the breast even though she is far advanced in her illness and cure is impossible. The chief areas of development since the application of estrogens and androgens in the palliative therapy of breast cancer are the controversy over radical surgery vs. simple mastectomy with intensive irradiation; the use of calcium excretion and endocrine assays in determining endocrine responsiveness and the proper treatment; the recognition of ovarian hyperplasia in menopausal women as a frequent endocrine background for the disease; the use of adrenocortical hormones in study and treatment; and the use of therapeutic adrenalectomy and hypophysectomy. Events at the menopause are important in the incidence of breast cancer. Five times as many women with cancer of the breast have late menopause as do normal women. Estrogen production in the postmenopause may reach surprisingly high levels, giving constant rather than the physiological periodic breast stimulation, particularly in ovarian cortical stromal hyperplasia. Urinary estrogen excretion may be increased forty-fold. Cancer of the breast is the first known instance of a malignant tumor being associated with an increase in production of its own growth stimulant. Prognosis is more grave in the male than in the female, owing to the facts that the tumor may go unchallenged for a longer period and that absence of fat promotes early lymphatic spread. Orchiectomy and estrogen administration may produce amelioration, just as estrogens are of value in the disease in postmenopausal women in the absence of endogenous estrogens. Lactation and nursing reduce the likelihood of later development of cancer of the breast. About 40 per cent of breast cancers in younger patients are shown with empirical success with oophorectomy or adrenalectomy to be estrogen stimulated, but with current criteria, as the stilbestrol test, practically all tumors in the young or menopausal age are estrogen stimulated. There is some evidence that some breast cancers are pituitary stimulated, and that others are hormone-independent. Route of spread of the tumor—direct extension, lymphatics, or blood stream—cannot be related to prognosis or treatment. Sites of spread are important—skeleton benign and viscera lethal. Speed of spread is all important, the slow tumors giving best response to endocrine therapeutic procedures. The following laboratory tests are useful in determining and following therapy: roentgen-ray examination of chest, spine and pelvis, FSH, estrogen, and mammotropin assays, blood and urine steroid assays, complete blood counts, blood electrolyte and protein profile, serum calcium concentration, serum alkaline phosphatase determination, calcium excretion studies, the stilbestrol-stimulation test, and the cortisone-inhibition test. Accurate and adequate surgery (mastectomy, castration, adrenalectomy, and hypophysectomy), endocrinology, and radiology are essential to curative and palliative therapy of breast cancer. No patient with metastatic or reactivated cancer of the breast has yet been cured, but there

is much to be offered even though cure is unattainable.

Jessiman, A. G., and Moore, F. D.: Carcinoma of the breast; the study and treatment of the patient. New England J. Med. 254:846-853, May 3; 900-906, May 10; and 947-952, May 17, 1956.

Detection of Asymptomatic Cancer

The cost of finding one case of cancer in the center for detection of cancer in the asymptomatic patient has been estimated at seven to ten thousand dollars. The general practitioner is most favorably situated for complete examination of a patient for the detection of early cancer. His office is the place where cancer is most frequently suspected and diagnosed. Most family physicians are capable of performing the diagnostic procedures necessary for a thorough examination. Unless the examination is thorough and complete the patient leaves the doctor's office with a false sense of security. Many a melanoma of the sole of the foot has been missed because the patient did not tell the doctor, and the doctor did not insist that the patient strip completely. Many cancers of the nasal, oral, and pharyngeal passages are missed for lack of use of the ordinary laryngoscopic mirror and flashlight. Palpation alone will detect a great proportion of early cancers—thyroid, breast, kidney, uterus, ovary, rectum, prostate, testicle, and musculoskeletal system. The earliest sign of prostatic cancer is elicited by digital palpation. To fail to do this test in a man past 50 years of age is negligence. Sigmoidoscopy, especially in men, and pelvic examination, including cytologic smears, in women are parts of routine physical examination. Laboratory procedures should include hematocrit, differential blood count, and urinalysis, including microscopic examination. And all patients should be impressed with the necessity of making an appointment for examination on every birthday anniversary.

Walsh, J. G.: A cancer examination for the asymptomatic patient. GP 14:82-85, Dec., 1956.

Relation of Thyroid Function to Cancer

Cancer can no longer be considered an autonomic pathological process. Castration, estrogen therapy, and adrenalectomy temporarily retard growth of prostatic cancer. Genesis and evolution of cancer may be profoundly influenced by hypo- or hyperfunction, spontaneous or artificial, of the testes, ovaries, adrenals, and pituitary. The role of thyroid function in the development of a heterogeneous cancer was investigated by surgical thyroidectomy, medical thyroidectomy with radioiodine, artificial hyperthyroidism by administration of thyroid or thyroxin, and by inducing hypothyroidism with antigoitrogenic synthetics. It is difficult to induce thyroid cancer in animals, and spontaneous cancers in animals are rare except in a rare breed of rats. Thiouracil predisposes to the genesis of dibenzanthracene sarcoma and thyroxin has the opposite effect. Thyroid hormone and the antithyroid drugs have restrictive or stimulating effects on experimental cancer by alteration of hormonal equilibrium. Total thyroidectomy and administration of antigoitrogenic drugs are dangerous in the cancer patient. Large doses of thyroxin inhibit growth of certain cancers, especially of the genitourinary system. Thyroid cancer is less malignant in children than adults because the child's thyroid is more active. All procedures increasing thyroid activity inhibit the growth of cancer, especially genital and mammary; and all procedures decreasing thyroid activity stimulate the growth of cancer. Treatment of any thyroid lesion should not be commenced before all possible diagnostic procedures give assurance of the absence of a potential extrathyroid cancer.

Desaive, P.: Observations cliniques en faveur de l'existence de relations entre la fonction thyroïdienne et le comportement de cancers hétérologues. [Clinical observations favoring the existence of a relation between thyroid function and the behavior of heterologous cancers.] Acta chir. belg. 55:25-49, Jan., 1956.

Hypophysectomy in Advanced Breast Cancer

Six cases of advanced cancer of the breast, in which other, less radical, procedures had proved useless, were treated by hypophysectomy. In two, the disease appeared to be arrested; the patients are

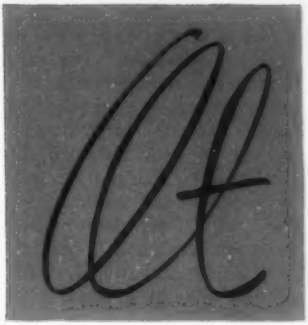
apparently healthy and happy, and are living normal lives with their families. A third patient, although the treatment was less successful, has been free from pain for a year, and has a more hopeful outlook. The other three patients died two, five, and seven months after hypophysectomy, which relieved two of their pain. Six additional cases are too recent for evaluation. The procedure has something to offer as a last resort.

Bethune, G. W.: Advanced breast cancer; a small series treated by hypophysectomy. Canad. M. A. J. 74:798-802, May 15, 1956.

Hormones and Breast Cancer

It is now considered that some cancers of the breast are dependent on estrogens and that prognosis in these cases will improve with removal of the estrogens, ovarian and adrenocortical. Simple androgen administration and ovariectomy were insufficient because after removal of the ovaries the adrenals hypertrophy and the secretion of estrogens is increased. With the advent of cortisone to compensate the loss of the adrenals it becomes logical to remove this supplementary source of estrogens as a palliative measure in breast cancer. If adrenalectomy is complete the estrogen-dependent cases show a rapid and dramatic improvement and a recession of tumor growth which may last several months. It is agreed that there is no means of determining which case depends on estrogens, and can be expected to improve under treatment, except trial of hormone therapy. This takes several weeks, but, if the tumor proves to be estrogen-dependent, there is a dramatic response one to six days after adrenalectomy. Old postmenopausal patients often show a spectacular temporary remission, particularly of soft-tissue lesions, after large doses of estrogens. Palliative therapy with estrogens and androgens was studied in 106 cases of advanced Stage-IV cancer of the breast. All had received all possible benefit from surgery and irradiation or were too far advanced for any but palliative therapy. Three women had had surgery alone, ten irradiation alone, eighty-two surgery and irradiation, and eleven no treatment. All were examined monthly or bimonthly according to their conditions and responses to treatment. In the author's experience small doses of stilbestrol are practically valueless. He recommends early doses of 5 mg. q.i.d. with increases to as much as 50 mg. q.i.d. if required. The patient must be impressed with the necessity of continuous dosage in the face of postmenopausal bleeding or gastrointestinal toxic effects. Increase in dosage usually controls the bleeding and the tolerance is usually improved by perseverance with the prescribed dosage. Some patients took 160-200 mg. of stilbestrol daily. Withdrawal bleeding is apt to occur if dosage is interrupted even for a day. Thirty patients on 5 to 50 mg., q.i.d., for as long as 125 weeks had no bleeding. Other complications of estrogen therapy were pigmentation of the nipples, areolae, linea nigra, perineum, and of senile keratoses, and edema of the ankles and lower legs. Fifty-seven patients were treated with androgens. Approximately one-third of these complained of nausea and vomiting. Signs of virilization occurred as follows: hirsutism, 58 per cent; voice changes, 45.5 per cent; enlarged clitoris, 26.3 per cent; acne, 19.3 per cent. The younger patients and those with osseous metastases were given only androgens. Most of the patients were given 300 mg. testosterone propionate by injection daily. Of the 106 patients, 55.5 per cent were living six months after starting hormone treatment, 31.2 per cent after one year, 11.6 per cent after two years, 4.7 per cent after three years and after four years, and 0.94 per cent after five years. Average age at beginning of therapy was 55 years, and mean survival was forty-eight weeks. Improvement was observed in 29 per cent of cases. Fourteen of the seventeen women who improved with androgens had their first symptoms before the menopause, and thirteen of the fourteen who improved with estrogens had their first symptoms after the menopause.

Foss, G. L.: Palliative hormone therapy of advanced mammary cancer; review of 106 patients studied in seven years. Lancet 1:651-656, May 12, 1956.



at a glance . . .

one-minute abstracts of the current literature on uterine cytology . . .

Early Diagnosis of Cervical Cancer

Since 1936 ambulatory cervical biopsies have been performed on nearly all outpatients, in the gynecological department of the Free Hospital for Women, Brookline, Mass., when the cervix has shown ectropion, erosion, eversion, laceration with eversion, and even a normal nulliparous cervix if the Schiller test is positive. It is a mistake to depend on any single one laboratory procedure for a diagnosis of carcinoma in situ of the cervix. A negative Papanicolaou smear should be followed by a Schiller test and biopsies. In a screening program the first vaginal smear yielded an accuracy of 70 per cent in diagnosis of carcinoma in situ; but the clinicians would have missed 26 of 119 patients with carcinoma in situ but for the positive cytological reports, because the cervix looked normal and biopsy was not considered necessary. In every woman more than 20 years of age the cervix should be carefully inspected, and routine smears taken. The cervix is then cleansed and stained with Gram's iodine solution, and, if abnormal, biopsies are taken. In discussion G. W. Mitchell, Jr. recommended prompt, sharp conization of the cervix following cytological diagnosis, and Ruth Graham stated that, at Vincent Laboratory, in contrast to the 70 per cent accuracy reported by Dr. Younge, 90 per cent of cases where the histological diagnosis of carcinoma had been made the lesions were discovered on the first cytological examination. Dr. Younge reported missing only 10 to 15 per cent of carcinoma in situ by the Schiller test.

Younge, P. A.: A gynecologist's evaluation of methods of early cancer diagnosis. In Homburger, F., and Fishman, W. H., Eds.: The Laboratory Diagnosis of Cancer of the Cervix. New York, S. Karger, 1956 pp. 16-20; disc. 21-22.

Office-Practice Cytology

Detection of carcinoma of the uterine cervix in the preinvasive stage has been greatly assisted by the inclusion of exfoliative cytology in the examination of the female pelvis. The simplicity of the method of collecting and fixing the smear lends itself well to use in the practitioner's office. Twenty general practitioners, nine gynecologists, and three internists in Saginaw County (Michigan) cooperated in a survey of patients in their private offices. Single specimens taken with a wooden spatula and fixed in ether-alcohol were mailed to the local health department for distribution to the pathologists. One thousand specimens were examined. One new case of cancer of the cervix was found, and four cases previously known were detected by the screening procedure. It is the authors' opinion that cytological smear technique has a definite place in the practitioner's office and that such facilities

should be expanded. The ready availability of slides and fixative solution in the physician's office and the accessibility of a cytologist would encourage such a practice. The cytological method serves a valuable role in raising suspicion of malignant process, in encouraging close surveillance of the gynecological patient with atypical cervical epithelium, and as an indication for repeated tissue evaluation.

Henderson, N. D.; Bucklin, R., and Volk, V. K.: Screening for carcinoma of the cervix; the use of the cytological smear in office practice. J. Michigan M. Soc. 56:461-464, April, 1957.

Cytology in Prognosis of Radiation Therapy

Cells in the vaginal smear showing increased density and vacuolization of the cytoplasm indicate the patient to be more sensitive to radiation than are patients who do not have such cells. If the percentage of these cells in the smear, determined like a differential blood count, is less than 10 the sensitization response is poor; if more than 10, good. Similarly, radiation response is determined at intervals by study of vaginal smears. A patient showing poor radiation response does very poorly if radiation is the only therapy. Response to roentgen-ray and radium therapy can be predicted from the radiation response as revealed in the vaginal smears.

Graham, R.: The cytologic prognosis in cancer of the cervix treated by radiation. In Homburger, F., and Fishman, W. H., Eds.: The Laboratory Diagnosis of Cancer of the Cervix. New York. S. Karger. 1956; pp. 31-40; disc. 44-45.

Cytology in Prognosis of Surgical Therapy

When the sensitization response is poor the patient may be expected to respond poorly to radiation therapy, and those patients with marked sensitization response may be expected to have a comparatively good prognosis. The reverse applies to patients treated surgically—those with good sensitization response have poor prognosis, and those with poor sensitization response attain a fairly satisfactory survival rate. This may be explained by the fact that patients with poor sensitization response tend to have a low incidence of regional metastases. The percentage of sensitization-response cells in the vaginal smear, therefore, gives an indication of the choice between surgical and radiation therapy. A poor radiation response can sometimes be changed to a good response by supplemental medication with α-tocopherol 100 mg. daily by mouth or testosterone propionate 25 mg. three times a week intramuscularly. In discussion Ruth Graham gave as an explanation of sensitization response that it is a localized immune response to the tumor. This explains why in the very early lesions, when host resistance is inadequate, the sensitization response is low, and why when host resistance fails in far advanced lesions, the sensitization response disappears.

Graham, J. B.: Cytologic prognosis in cancer of the cervix treated by surgery or radiation. In Homburger, F., and Fishman, W. H., Eds.: The Laboratory Diagnosis of Cancer of the Cervix. New York. S. Karger. 1956; pp. 41-44; disc. 44-45.

Tampon Cytology of Cervix

The Draghi tampon was evaluated as a means of collecting cellular specimens from the uterine cervix, and this method was compared with routine aspiration and scraping of the cervix. The tampon was left in the vagina twelve to sixteen hours. Upon removal its end was pressed upon three slides, fixed, and examined by conventional Papanicolaou technique. Seven hundred and sixty patients had negative histological, and negative tampon and routine, conventional cytological reports. Of the nineteen of twenty patients with atypical hyperplasia who had routine cytology, fifteen were suspicious or positive, and only two of the twenty had suspicious tampon specimens. There were thirteen patients with carcinoma in situ. All twelve of these who had routine cytology were suspicious or positive, and only six were suspicious or positive by the tampon method. Seventeen of the twenty-seven cases of invasive cancer had routine cytology; sixteen of these seventeen were suspicious or positive; twenty-four of the twenty-seven were suspicious or positive by the tampon method. Sixteen patients had endometrial adenocarcinoma. Of the

thirteen of these studied by routine cytology, six were suspicious or positive; eleven of the sixteen were suspicious or positive by the tampon procedure. The latter method was unsatisfactory in detecting hyperplasia and carcinoma in situ, but was about as satisfactory as the routine method in detecting invasive cancer, and possibly more satisfactory in endometrial adenocarcinoma. Improvements in the tampon itself, change in length of its retention, and in methods of transfer to slides may increase the reliability of this method.

Scott, R. B.; Brown, A. M., and Reagan, J. W.: Comparative results of the routine Papanicolaou and the Draghi tampon cytologic studies in atypical hyperplasia of the cervix and uterine cancer. Am. J. Obst. & Gynec. 73: 349-353, Feb., 1957.

Cytology—Opinion of Gynecologists

Sixty-one diplomates of the Board of Gynecology and Obstetrics in the Boston area, in response to a questionary, expressed the following majority opinions of the importance of cytology and of its influence on their clinical management of cervical cancer: (1) Routine annual physical examinations of all women past the age of 35 should include Papanicolaou smears. (2) Criteria for using cytologic studies when routine smears are impractical included any visible cervical lesion, abnormal bleeding, presence of clinical uterine tumor, and request of patient. (3) Cytology alone cannot distinguish between in situ and invasive cervical cancer. (4) Following a cytologic diagnosis of cancer in situ repeat smears, multiple biopsies, and sharp cone biopsy are indicated. (5) All untreated carcinomas in situ eventually become invasive according to one-half the gynecologists questioned. (6) During pregnancy cancer in situ diagnosed only by cytology is confirmed by biopsies, and when diagnosed histologically delivery would be awaited, hysterectomy performed, or radiotherapy instituted. Cytology was overwhelmingly recognized as a useful screening method that should be used in conjunction with biopsies. Unfortunately the cytologic methods developed by Papanicolaou cannot be used generally in population screening for lack of skilled manpower. Another obstacle to the general application of these methods to the diagnosis of cervical cancer is the confusion and ignorance that exist among physicians concerning their scope and limitations. Simpler methods of screening should be developed. Electronic scanning devices to facilitate the screening of the smears, and the determination of β-glucuronidase in the vaginal fluid are efforts aimed in that direction.

Homburger, F., and Fishman, W. H.: Introduction. In Homburger, F., and Fishman, W. H., Eds.: The Laboratory Diagnosis of Cancer of the Cervix. New York. S. Karger. 1956; pp. 5-8.

Cytological Research

Papanicolaou's original purpose forty years ago, in studying the cells exfoliating into the vagina of rodents was entirely unrelated to the detection of cancer or to any of the subsequent practical applications of the technique of exfoliative cytology. The original investigation was planned as a basic and purely morphologic study of the sex chromosomes in the female guinea pig. There was a need for a method of determining the time of ovulation. This method was found in the diverse cell forms and the sequence of distinctive cytologic patterns by which the vaginal, uterine, and ovarian cyclic morphologic changes and the exact time of ovulation could be determined accurately. The evolution of exfoliative cytology illustrates the value of a pure science—basic, fundamental research—with freedom of the investigator to follow a hunch wherever it may lead. In this practical age basic research is not always given its rightful share of recognition. This initially purely academic study of exfoliative cytology has blossomed into a variety of useful applications from more efficient animal breeding to preventive medicine.

Papanicolaou, G. N.: The evolutionary dynamics and trends of exfoliative cytology. [Bertner Foundation Award Lecture.] Texas Rep. Biol. & Med. 13:901-919, Winter, 1955.

Dissemination of Uterine Cancer

The first evidence for superficial dissemination of cancer of the body of the uterus through the tubes to the peritoneum

and ovaries is presented. This evidence consists of demonstrating by cytologic techniques cancer cells in the tubes and in the fossa of Douglas in the surgical specimens from twenty-seven cases of panhysterectomy, twenty-five for adenocarcinoma of the uterine body, one for sarcoma of the uterine body, and one for adenocarcinoma of the right tube with metastasis to the body of the uterus. No metastases in the tubes or ovaries were found in any of these cases. The tubes were irrigated, the washings were centrifuged, and the sediment smeared and examined by the Papanicolaou technique. In twenty of the adenocarcinoma cases washings were also obtained from the Douglas fossa by flushing with saline immediately after opening the abdomen. Tumor cells were found in the tubes in fifteen of the twenty-five cases of adenocarcinoma; and in the pouch of Douglas in six of the twenty cases. Best results were obtained by taking direct smears from the tubes and also examining the centrifuged washings. In the one case of sarcoma there were tumor cells in both tubes; and in the one case of carcinoma of the right tube with metastasis to the body of the uterus, tumor cells were found in the left tube. Some of the tumor cells found appeared to be fully viable and often occurred in groups, the form generally considered to be most capable of implantation. The superficial dissemination, therefore, affords a possibility, in addition to the lymphatic and blood-stream routes, for metastasis to the tubes and peritoneum.

Höeg, K.: Superficial dissemination of cancer of the uterine body. Cytological examination of smears from the tubes and the pouch of Douglas. J. Obst. & Gynaec. Brit. Emp. 63:899-902, Dec., 1956.

Cervical Smear as Screening Test

At Grady Memorial Hospital, Atlanta, during one month 670 patients, 218 white and 452 nonwhite, were examined by routine smears obtained by scraping the cervix with a wooden tongue blade. Forty of the 670 smears were reported "malignant." During the month of study eighty-four patients had four-quadrant biopsies of the cervix. Ten of these were positive five invasive and five in situ carcinoma. The smears of nine of these ten patients were positive. Among the total 670 patients examined, seven with invasive and eleven with in situ carcinoma were found by the cytological technique. Of six patients with carcinoma in situ diagnosed because of the smear, five were less than 26 years of age. No patient with carcinoma in situ diagnosed by other means was less than 26 years old. Survey of the Atlanta area revealed but one gynecologist in private practice who takes routine vaginal smears from each patient regardless of complaint or age. Most physicians used smears only on definite indications, and others did not use cytological techniques. Cytology, together with cervical and endometrial biopsies and the Schiller iodine test, constitutes the "ideal" method of detecting malignant pelvic neoplasms.

McClure, J. H.; Caton, W. L., and Lucchese, G.: The use of the routine vaginal smear as a screening test for uterine carcinoma. J.M.A. Georgia 45:305-308, July, 1956.

Vaginal Cytology in Cancer of the Fallopian Tubes

Four of five cases of primary carcinoma of the Fallopian tubes previously reported showed positive Papanicolaou vaginal smears. In the case described here cancer of the uterus was eliminated by histologic examination of specimens from endometrial curettage. Vaginal smears were persistently positive and laparotomy was performed. Primary adenocarcinoma of the left Fallopian tube was found. This tumor would have been overlooked if the examination had been limited to curettage. Papanicolaou smears can be of significant diagnostic aid in detection of carcinoma of the Fallopian tubes.

Larsson, E., and Schooley, J. L.: Positive vaginal cytology in primary carcinoma of the Fallopian tubes. Am. J. Obst. & Gynec. 72:1364-1366, Dec., 1956.

Gynecologic Cytology

An estimate of the value of cytology is made from an analysis of the results of examination of 3337 smears from 2250 gynecologic patients of a service not spe-

cially engaged in cancer detection or therapy, at the University of Birmingham, England. Contrary to the usual American method of initial screening by personnel responsible only for eliminating definitely negative smears, the cytologist of this group, and in time her technicians were made responsible for their own reports—Classes I to V, Papanicolaou. Not less than six months training was necessary for them to become proficient. One of the authors spent seven months working intensively in cytology in the United States and returned to train technicians as cytologists, not as screeners. To read a vaginal smear requires an average of seven to ten minutes. A cytologist may suffer eye strain after four hours or less. From fifteen to eighteen slides is a day's work for a cytologist. Novak's estimate of 500 hours work to reveal one carcinoma is considered low. The cost of finding a single case of carcinoma in situ by screening groups of well women has been quoted as $110 by Ayre, $500 by Hertig, and prohibitive by Lombard. Every patient in this group with a positive smear was investigated further by curettage of the uterine body and endocervix and by ring biopsy of the cervix, including the squamocolumnar junction and much of the lower cervical canal. The cytological were compared with the histological findings. The cervical tissues were classified as benign, carcinoma and carcinoma in situ—typical or equivocal. Among the 2250 patients examined, the cytological method was responsible for finding one case of invasive carcinoma of the cervix, eight cases of carcinoma in situ, and one case of carcinoma of the cervix. Of all smears, 0.5 per cent were falsely positive and 0.26 per cent, falsely negative. It is concluded that cytology may very occasionally lead to the diagnosis of unsuspected carcinoma of the cervix, that in confirming the presence of carcinoma of the cervix the method is accurate, and that it provides an opportunity to study the natural history of carcinoma in situ of the cervix.

McLaren, H. C.; Taylor, C. W., and Attwood, M. E.: The value of cytology in gynaecology. J. Obst. & Gynaec. Brit. Emp. 63:801-811, Dec., 1956.

Beta-Glucuronidase Screening Test

The determination of β-glucuronidase in vaginal fluid makes possible, by a single chemical procedure, the segregation of premenopausal women in whom there is a high probability of neoplastic disease. These can then be subjected to intensive cytological and histological study with a minimum of effort and economic loss. This method of mass screening requires only the services of an average laboratory technician in contrast to the cytological screening that requires specially trained technicians and pathologists. The test is no more expensive than a Papanicolaou smear. Values of 400 units β-glucuronidase per gram of vaginal fluid are found in 80 per cent of premenopausal women with cervical cancer. This makes the test practical for screening gynecological populations. Homburger, in concluding remarks, stated that this enzymological method, though not yet widely used, is perhaps the cheapest and most practical screening procedure for cervical cancer in premenopausal women yet available.

Kasdon, S. C.: Clinical aspects of vaginal fluid beta-glucuronidase activity in the diagnosis of cervical cancer. In Homburger, F., and Fishman, W. H. Eds.: The Laboratory Diagnosis of Cancer of the Cervix. New York, S. Karger, 1956; pp. 59-65; disc. 65-67.

Pelvic Cytology after Age 65

At the Cancer Prevention Clinic of Chicago, 209 apparently well women 65 years of age or older were given complete physical examinations including cervical smears by the Papanicolaou method. One in twenty-three of these women had cancer: two of the genital tract, four of the rectum, one of the breast, one of the bladder, and one of the skin of the face—a total of nine cases of cancer, two revealed by cytology.

Farley, D. M., and Wolff, J. R.: Pelvic findings in women past the age of 65. J. Am. Geriat. Soc. 4:1-7, Jan., 1956.

Cervical Cytology and Prognosis

In 1944 in the Sohlgren Hospital, Gothenburg, Sweden, 18 per cent of patients with cancer of the cervix were in the first stage when first seen; ten years later, this

figure had risen to 38 per cent. One of the reasons for this improvement in early detection is that in 1950 the hospital's cytological department was founded. The overall five-year–cure rate for a series of 459 patients in the period 1944 to 1948 was 50.8 per cent, and for patients in the first stage it was 79 per cent. In a group of 257 patients with cancer of the cervix, 6 per cent false-negative smears were obtained. The number of false-positive smears varies with the degree of discrimination shown by different observers. Cytological test revealed cancer of the uterus in 0.5 per cent of the women examined.

Leissner, H.: Cancer of the cervix. [Foreign Letter.] J.A.M.A. 163:676, Feb. 23, 1957.

Cytology in Cervical Cancer

At Johns Hopkins Hospital from 1947 to 1954, 5617 women were studied by cervical smear, vaginal smear, and biopsy. Of this group, 4735 (84.3 per cent) had normal smear and biopsy; 216 (3.8 per cent) were diagnosed as having cervical cancer by both smear and biopsy. There were 6.7 per cent of doubtful smears, 2.2 per cent false-positive, and 0.6 per cent false-negative smears. Of those women with doubtful smears, 12 per cent were shown to have cancer and 20.5 per cent to have basal-cell hyperactivity in the biopsy. In the 310 proved cases of cervical cancer, the initial smear was positive in 71.6 per cent, and doubtfully positive in an additional 14.5 per cent—an accuracy of 86.1 per cent for the initial smear, compared to 95.8 per cent accuracy for the biopsy. The greatest value of the cytological method is in the detection of early lesions and should be used in screening for detection of lesions in the grossly normal cervix. False-positive smears often show basal-cell hyperactivity in the biopsy and such patients require follow-up. The biopsy and the cervical smear should be used complementarily. Treatment should not be based on a single positive smear. Multiple biopsies should be made.

Vesbitt, R. E. L., Jr., and Brack, C. B.: Role of cytology in detection of carcinoma of the cervix. J.A.M.A. 161:183-188, May 19, 1956.

Early Cytological Diagnosis

Over a period of eighteen months at Groote Schuur Hospital, Cape Town, 2150 smears from 1050 patients were examined for malignant cells, for estrogenic dysfunction, and for chromosomal sexing. From the experience gained it is concluded that, taken as an adjunctive and complementary aid to tissue biopsy, exfoliative cytology has a very definite place in gynecology. Two smears were taken from each patient, one by aspiration from the posterior-fornix pool and one by scraping the cervix with a spatula. After the smears were taken the cervix was cleaned and examined macroscopically and, in many cases with the colposcope, giving particular attention to the mucocutaneous junction—the commonest site for incipient cancer. Various techniques, including silver and fluorescent stains and phase-contrast microscopy have been tried, but the authors prefer the Papanicolaou techniques of fixing and staining the smears. Diagnostic curettage and cervical-cone biopsy were performed when the smear was positive or suspicious. Cytological criteria of malignancy include variation in nuclear size, shape and depth of staining; unequal and distorted nuclei in multinucleate cells; increase in cell size, gross abnormalities of cell shape, and vacuolization. This method permits the detection of preinvasive cancer, when the earliest, best, and curative treatment can be instituted.

Constantine, N. D., and Moore, D.: The diagnosis of early genital cancer and other abnormalities by cytology; a pilot survey. South African M.J. 30: 1201-1209, Dec. 15, 1956.

Cytology and Colposcopy

The cytologic smear is now established as a reliable aid in the detection of asymptomatic gynecologic cancer. Colposcopy, direct visualization of the cervix under magnification also is of value in detecting malignant conditions of the cervix, vagina, and vulva. The findings by cytology and colposcopy in twenty-eight cases of untreated cervical carcinoma were compared: eight cases in Stage I, nine in Stage III, and three in Stage IV were all de-

tected by both methods; eight cases in Stage II were all detected by cytology and all but two (which were endocervical) by colposcopy. Correlation between cytologic smear and histologic findings is not always definite, and the same is true with colposcopy. Cytology is more apt than colposcopy to detect endocervical cancer, and is more specific for portio cancer; but colposcopy is more efficient in detecting epithelial atypia. Both methods are helpful in selecting cases for biopsy. Colposcopy points out the site for biopsy and for cytologic study. By the concurrent use of the two methods abnormal epithelial changes are detected earlier.

Lang, W. R., and Rakoff, A. E.: Colposcopy and cytology: comparative values in the diagnosis of cervical atypism and malignancy. Obst. & Gynec. 8: 312-317, Sept., 1956.

Vaginal Cytology in Extrauterine Cancer

Positive vaginal smears, taken in the hospital ward or at autopsy, were found in ten cases of primary cancer of breast, anus, kidney, ovaries, Fallopian tubes, and stomach with involvement of ovary. There was no evidence of metastasis to uterus or cervix in any of these cases, and there had been no significant gynecological complaints. Many tumor cells were seen free in the tubes in those cases which did not involve the tubes. The vaginal smears showed clusters as well as free cells. It seems obvious that well-preserved tumor cells can be carried into the tube by direct extension, from metastatic tumor to the ovary or tube, by ascitic fluid, or by ameboid movement of the cells themselves. The cells are then carried through the tube by peristalsis and epithelial ciliary movement, through the uterine cavity to the vaginal pool where they are picked up in the smear. It is not possible as yet to determine the primary source of the tumor by examination of the smear alone; but, when the vaginal smear is positive and repeated biopsies of the cervix and endometrium are negative, a primary extrauterine tumor should be sought.

Song, Y. S.: The significance of positive vaginal smears in extrauterine carcinomas. Am. J. Obst. & Gynec. 73:341-348, Feb., 1957.

Cytology—Fluorescence Technique

Acridine-orange, fluorescence-microscopic technique permits rapid scanning in exfoliative cytology. Most malignant cells obtained in vaginal and cervical smears yield fluorescent pictures strikingly different from those of normal cells. The cytoplasm is brilliant orange-red of a very intense hue, and the nuclei are intensely yellow-fluorescent with brilliant orange-red nucleoli. The acridine-orange technique, even under low power, shows the malignant cells in brilliant colors, making possible the rapid elimination of negatives in screening; and under high power the fluorescent colors strongly enhance the contrasts, making possible an excellent evaluation of the morphological criteria. The technique is suggested for rapid scanning, to be followed, when indicated, by examination under high power and by other procedures for differential diagnosis of suspected cells.

von Bertalanffy, L.; Masin, F., and Masin, M.: Use of acridine-orange fluorescence technique in exfoliative cytology. Science 124:1024-1025, Nov. 23, 1956.

Tampon Smear in Endometrial Cancer

Tampons were inserted into the vagina in the evening and recovered next morning at which time stamp smears were made upon slides which were immediately immersed in fixative solution. The slides were examined by Doctor Papanicolaou who cautioned against misinterpretation of tampon smears showing a profusion of histiocytes as is often the case in resolving infections or, normally, during the postmenstrual phase. Under these conditions the smear may show histiocytes exhibiting pronounced vacuolation and engulfment of polymorphonuclears, simulating adenocarcinoma cells. There were three false negatives in a series of twenty-three cases. Accuracy of the test was 87 per cent. This study parallels previously reported observations concerning carcinoma of the cervix.

Brunschwig, A.: Detection of endometrial adenocarcinoma by tampon-smear method, with comments on cytology of tampon smears by George N. Papanicolaou, M.D. Cancer 10:120-123, Jan.-Feb., 1957.

The Cancer-Diagnostic Potential of Uterine Exfoliative Cytology

George N. Papanicolaou, M.D., Ph.D.

The cytologic diagnosis of cancer of the female sex organs is based on the microscopic examination of smears prepared from the fluid contents of the vagina, the cervical canal, and the endometrial cavity. A thorough exploration aimed at optimal results would thus require three types of smears—vaginal, cervical, and endometrial. Each of these may be accredited with some points of superiority over the others.

Smears prepared from fluid aspirated from the vagina contain cells exfoliated largely from the vagina and the ectocervix, and to a lesser extent, from the endocervix and the endometrium. Their particular value is that they provide information pertaining to the cyclic changes in the morphology of the uterovaginal epithelium, the action of hormonal factors upon the accessory female sex organs, and the bacterial and parasitic flora of the vagina. On the other hand, a better sampling of cells derived from the ecto- and endocervical epithelium and the endometrial mucosa is provided by endocervical or endometrial smears.

Techniques of Preparing, Preserving and Staining Smears

In this discussion, description of techniques is confined to those currently employed in our laboratory. Others will be only briefly mentioned.

Material for a vaginal smear can be obtained with the aid of a pyrex glass pipette equipped with a strong, tightly fitting rubber bulb. The pipette now in use in our laboratory is approximately 5 inches long and ¼ inch in diameter and is slightly curved about 2 inches from its rounded tip. A sterilized pipette, with the rubber bulb so compressed as to prepare a vacuum, is introduced gently into the posterior fornix of the vagina. While the bulb is being slowly released the pipette is cautiously rotated to facilitate the aspiration of as large an amount of secretion as possible. The pipette is then withdrawn, its content expressed by means of a sudden pressure on the bulb, and spread with the convex side of the pipette upon the surface of a clean glass slide. A small label written in lead pencil giving the name of the patient, type of smear, and date is attached to each slide by a paper clip.

In order to secure good fixation the smear is promptly immersed in a solution of equal parts of 95 per cent alcohol and ether, contained in a wide-mouthed bottle, 1¾ x 1¾ x 4½ inches. Fixing the smear before drying is very important, since cells exposed to drying before fixing are poorly preserved and markedly distorted. Smears are fixed within minutes in the alcohol-ether mixture. However, a fixation of an hour or longer permits a more thorough penetration of the cells and increases the adhesion of the smear film to the slide. Smears which cannot be stained immediately can be preserved in the alcohol-ether solution for several days or even weeks with little, if any, deterioration. A woman should refrain from douching or bathing for several hours prior to the taking of a smear.

Vaginal smears can be taken by a nurse or even by a properly instructed patient, but cervical, endocervical, and endometrial smears must be taken by a physician since they require instrumentation. A cervical smear can be prepared with secretion obtained from the mouth of the cervix either by aspiration or by the use of a

From the Papanicolaou Research Laboratory, Department of Anatomy, Cornell University Medical College, New York, N. Y.

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cotton-tipped applicator or a wooden spatula.[1] The main advantage of the cervical smear is that it provides richer cellular material from the region of the squamocolumnar junction, which is considered the most frequent site of origin of carcinomas in the uterine cervix.

Material for the endocervical or endometrial smear can be aspirated from the endocervical canal or the uterine cavity by means of a thin, flexible, metal cannula. A laryngeal cannula may serve this purpose, though one can make use of one of the several specially constructed cannulae, some of which have side perforations, or are equipped with a retractile brush.[2, 4, 5] Endocervical and endometrial smears are of great value in the detection of adenocarcinomas of the cervix or the endometrium. A detailed description of the endometrial aspiration technique is given elsewhere.[9]

The spreading of the aspirated endocervical or endometrial fluid upon the slides follows the rules already described for the vaginal smear. Since endocervical and endometrial smears tend to dry faster than vaginal, the prompt immersion of the slides in the alcohol-ether fixative is strongly suggested. Another reason for the immediate fixation of such smears is the fact that drying causes a severe distortion of the mucus-secreting cells of the endocervical or endometrial epithelial lining, whereas its effect upon the squamous cells derived from the epithelium of the ectocervix or vagina is much less noticeable.

The need for immediate fixation of the smears and their preservation within the fixing fluid until the time of staining, has been a serious drawback to the wider utilization of the cytodiagnostic method. Since mailing a bottle containing an inflammable fluid like alcohol-ether is prohibited, the smears have to be brought to the laboratory in person. This limits the use of the method to areas in the vicinity of a cytology laboratory.

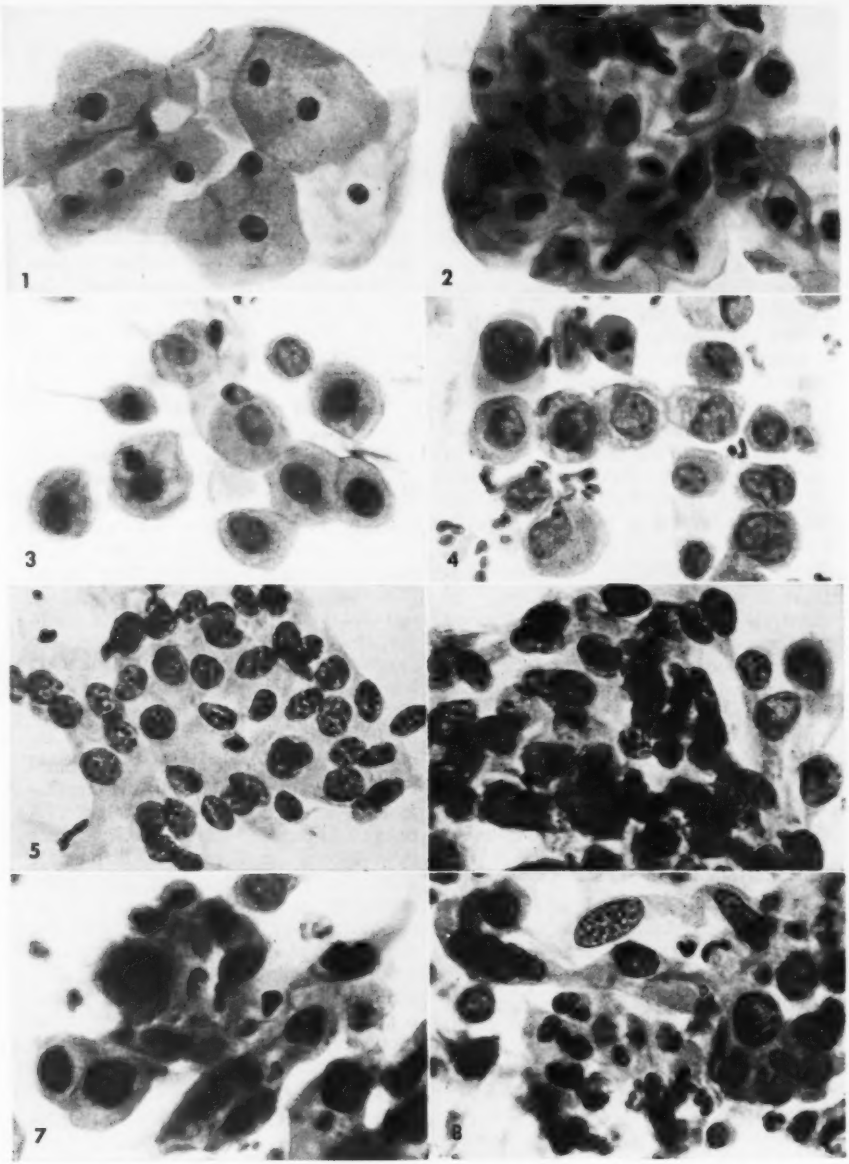
To overcome this handicap several ways for protecting smears from deterioration during mailing have been proposed. Of these, the one which has found wide application has been the glycerine technique.[3] Another method consists in drying the smears as soon as taken, wrapping them in wax paper, and mailing them to the laboratory where they are rehydrated by special procedures.[6] Such rehydrated smears can be fixed subsequently in alcohol-ether or other fixatives, but they do not seem to recover fully from the adverse effects of drying. The deterioration, as stated above, is much more pronounced in the endocervical and endometrial than in the cornified and keratinized cells of the vagina and ectocervix, which show greater resistance to drying.

A method providing adequate protection to all these cell types through prompt fixation and the formation of a covering film which would prevent drying was proposed in 1954.[10] This method has been used periodically in our laboratory for several years with gratifying results. Its technical aspects have more recently been subjected to a strict test in a special study directed toward the development of a simple and well standardized procedure that would be suitable for utilization on a larger scale. The results of this investigation are given in the following quotation from an article now in press:[11]

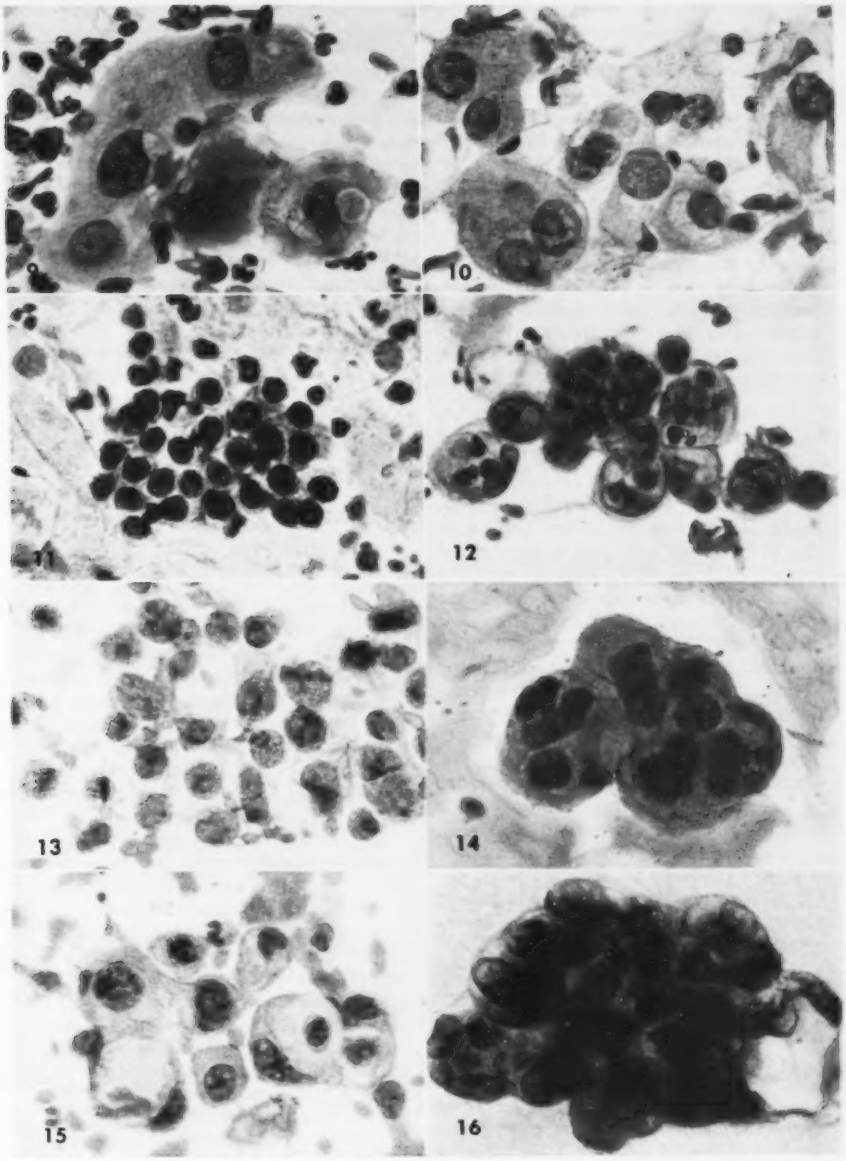
"Fresh, wet smears are covered immediately with a small quantity (approximately ¼ or ½ cc. per smear) of diaphane* solution (3 parts of 95 per cent ethyl alcohol to 2 parts of diaphane). After the diaphane has dried thoroughly, requiring 20 to 30 minutes, a hard, smooth film protects the surface of the smear. The slides can then be wrapped in wax paper and mailed any distance. When received in the laboratory, they are placed in alcohol-ether for approximately 20 minutes to remove the diaphane and then are stained according to the routine method for cytologic smears.

"The fixation, preservation, and staining of all types of cells in smears from female-genital and respiratory secretions were found to be very satisfactory even after a lapse of two weeks. Previous use

*Registered trade name of Will Corporation, Rochester, N. Y.



1. Normal superficial squamous cells. Vaginal smear.
2. Dyskaryotic cells of the superficial squamous type. Cervical smear.
3. Normal parabasal squamous cells. Vaginal smear.
4. Dyskaryotic cells of the parabasal squamous type. Cervical smear.
5. Normal endocervical cells. Vaginal smear.
6. Dyskaryotic cells of the endocervical type. Cervical smear.
7. Advanced carcinoma of the cervix, squamous-cell type. Cervical smear.
8. Advanced carcinoma of the cervix, endocervical-cell type. Vaginal smear.



9. Atypical (nonmalignant) cells from a case of trichomonas infestation. Cervical smear.
10. Atypical (nonmalignant) cells from a case of erosion of the cervix. Cervical smear.
11. Normal endometrial cells. Vaginal smear.
12. Adenocarcinoma of the endometrium. Vaginal smear.
13. Sarcoma of the uterus. Cervical smear.
14. Adenocarcinoma of the endocervix. Vaginal smear.
15. Adenocarcinoma of the tube. Endometrial smear.
16. Cystadenocarcinoma of the ovary. Endometrial smear. (×600)

of the method has shown that the staining of the cells remains unaltered for several years. Another favorable point is that the pouring of diaphane over a glass slide held in a horizontal position helps in the better spreading and the improved adhesiveness of the smear which thus tends to be more cellular."

If excess water is present in the specimen the diaphane film on the smear may appear milky and opaque instead of clear. Smears prepared from such specimens should, therefore, be adequately dehydrated in 95 per cent alcohol for one or two minutes before the use of diaphane.

The selection of the staining procedure to be used for smears prepared from the secretions of the organs of the female genital tract depends upon the purpose of study. Several methods have been proposed and are now in use for the evaluation of the female sex cycle or of problems related to pregnancy, fertility, and the action of sex hormones. Some of these methods are based chiefly on a differential staining of the cytoplasm permitting an appraisal of the degree of cornification or keratinization of the squamous cells found in the vaginal smears. This, useful as it may be for the identification of the different types of exfoliated squamous cells, is superseded by the particular importance of the structural modifications of the nucleus when the diagnosis of cancer is under consideration. A staining method designed primarily for the purpose of detecting and identifying malignant cells in smears, in addition to an adequate differential staining of the cytoplasm, should provide a good and sharp staining of the chromatin components of the nucleus. A high translucence of the smear, permitting a clear view through areas of overlapping cells or of cells covered with mucus or blood, would also be a very desirable feature. A method devised to fulfill these requirements is the OG-EA method described in 1942,[7] which has since found an extensive use in cytologic cancer diagnosis.

Instructions for the preparation of the staining solutions are given in the *Atlas*.[10]

Screening and Interpretation of Smears—Formulation of Cytologic Findings

The technical procedures used in the preparation and staining of smears are rather simple and can be taught in a relatively short time, but—and this is perhaps the most serious drawback of the cytologic method—the screening and evaluation of the cytologic preparations are time-consuming and require adequate training and long experience. In response to the steadily increasing need for trained personnel in this new diagnostic field special courses have been instituted in several cytology and pathology laboratories. During these courses instruction is given to cytotechnologists, who are now generally entrusted with the preliminary screening, and to medical doctors in whose hands the responsibility of the final diagnosis rests. It is felt that the time necessary for acquiring proficiency in this field, including completion of a special course in a qualified cytology laboratory, is at least one year.

Special caution should always be exercised to avoid false-positive reports. Nothing causes more harm to the reputation of the cytologist and the method itself or more confusion and concern to the clinician and the patient than a cytologic diagnosis positive for carcinoma, which has not been confirmed by a subsequent biopsy, curettage, or hysterectomy.

One should bear in mind, however, that unconfirmed positive-cytologic reports are not necessarily false positives, since they may be correct, and yet the malignant lesion may not be present in the relatively limited number of sections routinely examined in a pathology laboratory. There are cases on record in which a subsequent examination of a larger number of histologic sections has proved the presence of an early carcinoma, which was not to be seen in previous sections. In other instances negative interpretations of histopathologic sections rendered by a pathologist have been later modified or even reversed by the same pathologist. The issue should, therefore, no longer be that of cytology versus pathology but of positive versus negative findings. The latter should

STAINING TECHNIQUES

Detailed steps in the staining procedure as currently used in our laboratory are given below. The alternate procedure has the advantage of being shorter.

I. STANDARD METHOD

Fixation in equal parts of 95% ethyl alcohol and ether for at least 15 minutes.

80% alcohol

70% alcohol

50% alcohol

Distilled water

Harris hematoxylin, 6 minutes. (Prepare from standard Harris hematoxylin formula but omit the glacial acetic acid. Dilute stock solution with an equal volume of distilled water before using.)

Distilled water

Distilled water

Dip in 0.25% aqueous solution of hydrochloric acid, 6 dips

Running tap water, 6 minutes

Distilled water

50% alcohol

70% alcohol

80% alcohol

95% alcohol

OG 6, 1½ minutes

95% alcohol

95% alcohol

95% alcohol

EA 36 or EA 50, 1½ minutes

95% alcohol

95% alcohol

95% alcohol

100% alcohol

100% alcohol

Equal parts of 100% alcohol and xylol

Xylol

Xylol

Xylol

Mounted in neutral mounting medium (Permount)

II. ALTERNATE METHOD

Alcohol-ether (equal parts) for fixation or to dissolve diaphane solution film (15 minutes for the latter)

80% alcohol
70% alcohol
50% alcohol
Distilled water

Harris hematoxylin (full strength) acidified with glacial acetic acid (4 cc. per 100 cc. hematoxylin). Stain for ¼ to 1 minute depending upon the freshness of the stain; usually ½ minute is satisfactory.

Distilled water
Distilled water
Distilled water

(Additional distilled water washes may be added if necessary to remove all excess hematoxylin. This may be required when a large number of smears are being stained at one time.)

50% alcohol

Ammonium hydroxide, 1.5% solution in 70% alcohol, 1 minute

70% alcohol
70% alcohol
80% alcohol
95% alcohol
OG 6, 1 minute
95% alcohol
95% alcohol
95% alcohol
EA 65, 1 minute
95% alcohol
95% alcohol
95% alcohol
100% alcohol
100% alcohol

Equal parts of 100% alcohol and xylol

Xylol
Xylol
Xylol
Mounted in neutral mounting medium (Permount)

NOTE: Leave smears in solutions (alcohols) until the liquid runs off the slides in a smooth, clean sheet. If they are removed too soon, rivulets will show on the slide surface.

never be considered as conclusive. No patient should be fully reassured on the sole strength of a negative cytologic report.

A good understanding between the clinician and the cytologist on the formulation, classification, and interpretation of cytologic reports is of paramount importance. There are two systems of classification which are most commonly used at the present time. In many laboratories microscopic-smear findings are classified into three groups: negative, suspicious, and positive for carcinoma. In others, including ours, the findings are grouped into five classes: I, II, III, IV, and V. These two systems do not differ as much as they may seem to at first. Classes I and II correspond to the negative of the three-group classification, Class III to the suspicious, and Classes IV and V to the positive. The subdivision of the negative group into Classes I and II was motivated by the desire to make a distinction between strictly negative smears (Class I) and those in which atypical cells indicating the presence of a benign neoplasm or a severe inflammatory condition may be observed (Class II). The division of the positive group into Classes IV and V, on the other hand, serves the purpose of giving to the clinician more exact information on the degree of positive cytologic evidence in a given case. Class V designates conclusive positive findings, whereas Class IV, though indicative of a malignant neoplasm, expresses a somewhat more reserved attitude. The fact that our statistics and those of other laboratories using this system of classification show a very high accuracy in the Class V reports, approaching the optimum level of 100 per cent, gives great reassurance to the surgeon who is faced with a decision for or against an operative procedure. Though our policy is not to recommend major surgery on the basis of a Class V smear without confirmatory clinical or pathologic evidence, the surgeon may sometimes deem it necessary to proceed with an exploratory operation, when this appears to give the best chance for saving the life of the patient. Many early or concealed carcinomas have thus been brought to light.

Criteria of Malignancy

It has often been stated that the cytologic diagnosis of malignant neoplasms is based chiefly on aberrations and abnormalities in the structure and appearance of cells as seen in the exfoliated state in smears from different body fluids. There is much truth in this statement; yet one might safely state that a thorough knowledge of the normal exfoliative cytology of the various organs of the body and the range of its variability under various nonmalignant conditions is no less important. The lack of this knowledge is, perhaps, one of the most frequent sources of false-positive interpretations. One might even be tempted to attribute, at least in part, the absence of a self-asserting attitude on the part of the exponents of exfoliative cytology in earlier years to the lack of proper appreciation of this principle. The revival in this field came about as a result of long and meticulous studies on the normal exfoliative cytology of the female genital organs—first in animals and later in women.

The normal cells found in vaginal, cervical, and endocervical smears differ according to their site of origin. The ones derived from the epithelium of the vagina and the ectocervix are of the squamous type. Those exfoliated from the endocervix are of the secretory or glandular type. Figures 1, 3, and 5, illustrate three varieties of normal cells, the superficial-squamous (Fig. 1), the parabasal-squamous (Fig. 3), and the endocervical (Fig. 5).

In the early developmental stages of a malignant neoplasm of the cervix, the exfoliated cells can still be recognized as to their type and site of origin. The structural abnormalities characteristic of a malignant change are more or less confined to the nucleus. These abnormalities consist chiefly in a disproportionate nuclear enlargement, hyperchromasia, irregular distribution of the chromatin, and bi- or multinucleation. The cells illustrated in Figures 2, 4, and 6, are from cases of intraepithelial carcinoma or carcinoma in situ of the uterine cervix. In Figure 2, the

cells are of the superficial squamous type, the ones of Figure 4 are of the parabasal-squamous type, and those of Figure 6 are of the endocervical type. For designating such distinctly abnormal nuclear features the term "dyskaryosis" has been suggested. Depending upon the relative predominance of these atypical cell forms in a smear several dyskaryotic patterns may be recognized, such as the superficial-squamous (Fig. 2), the parabasal-squamous (Fig. 4), and the endocervical (Fig. 6). In most instances the various patterns appear intermixed, which indicates that they actually represent the same basic abnormality. However, each apparently has a different diagnostic and prognostic significance. In the majority of cases with endocervical- or parabasal-cell dyskaryosis the course of the disease is, as a rule, progressive and the histopathologic diagnosis is usually positive for an intraepithelial or early invasive carcinoma (Grade 0 or 1), whereas, in superficial-cell dyskaryosis there is sometimes regression and the histopathologic findings may not be positive for cancer. Cases of dyskaryosis are usually reported as Class III in our laboratory.

In the advanced stages of malignancy, the cellular and nuclear abnormalities, as seen in the exfoliated cells, are much more pronounced. The cells tend to acquire aberrant and bizarre forms making almost impossible the recognition of their basic type (Figs. 7 and 8). They also tend to form conspicuous clusters, which provide more conclusive diagnostic criteria, such as irregularity of pattern, anisocytosis, anisokaryosis, crowding, and loss of the lines of demarcation between the individual cells. As a result of these changes the original type of the cells can no longer be recognized except in a few cases in which a distinction between a squamous (Fig. 7) and an endocervical (Fig. 8) pattern is still evident. Since there is no single criterion by which the presence of cancer can be established with absolute certainty the diagnosis must necessarily be based on several of the above mentioned criteria.

Certain conditions like chronic cervicitis, trichomonas or mycotic infections, erosions, polyposis, condylomas, and other pathologic manifestations may produce cytologic changes simulating those of cancer. Nuclear enlargement beyond normal limits (karyomegaly) is perhaps the most common atypia observed in these conditions. When combined with hyperchromasia it may easily lead to an erroneous positive interpretation. A group of atypical cells with large and irregular nuclei from a case of trichomonas infection is shown in Fig. 9.

In cells of the superficial-squamous type, karyomegaly coupled with nuclear hyperchromasia produces a pattern greatly resembling that of superficial-cell dyskaryosis. Many a false-positive cytologic report has been given because of such an atypical pattern, which appears more frequently in smears taken during pregnancy. In a large percentage of such cases this abnormal pattern proved to be reversible, disappearing soon after the end of gestation.

In erosion (Fig. 10) a characteristic change which greatly facilitates its diagnosis is the increased exfoliation of endocervical cells, some of which may exhibit a typical palisade pattern, while others may assume a characteristic stout form. Bi- or multinucleation and occasionally the presence of small papillary fronds detached from the eroded area are also of diagnostic value. An accentuated endocervical exfoliation with many columnar cells and small polypoid fragments may often be seen in cases of endocervical polyps or a polypoid hyperplasia.

Adenocarcinoma of the Endocervix

The exfoliative cytology of the adenocarcinomas of the endocervix is closer to that of the adenocarcinomas of the endometrium than to that of the carcinomas of the endocervix. The configuration of clusters of cells exfoliating from the tumor area follows the well outlined and sharply circumscribed pattern often seen in adenocarcinomas of the endometrium and other organs. Figure 14 illustrates such a cluster from a case of endocervical adenocarcinoma. The eccentric position of the nuclei

and the vacuolation of the cytoplasm reveal the glandular type of the cells. When such cells are found in an endocervical aspiration smear their endocervical origin can be assumed with greater confidence than when picked up in a vaginal smear. The similarity in the grouping pattern of adenocarcinoma cells derived from different parts of the female genital tract often makes difficult the decision as to whether they are of endocervical, endometrial, tubal, or even ovarian origin. Their differentiation from cervical carcinomas can be made more safely.

Adenocarcinoma of the Endometrium

The exfoliative cytology of the endometrium, both normal and malignant, is not as well known as that of the cervix. Normally endometrial cells are carried through the cervical canal into the vagina only when menstrual or other bleeding occurs. Since adenocarcinoma of the endometrium is, as a rule, accompanied by bleeding (unless there is cervical stenosis or occlusion), malignant cells and cell clusters, in the majority of cases, find their way into the vagina and can thus be detected in vaginal or cervical smears. However, the diagnosis of endometrial adenocarcinoma by vaginal or cervical smears alone has not proved to be fully satisfactory. The identification of endometrial cells in such smears presents greater difficulties than of the more conspicuous vaginal and endocervical cells and requires a much more thorough screening of the slides. The wider use of the endometrial smear, which is gradually gaining favor among gynecologists, is bound to increase considerably the accuracy in the diagnosis of fundal adenocarcinomas. It will also provide more adequate material for the detection of early asymptomatic malignant lesions of the endometrium. Due to the present limited use of this smear type the exfoliative cytology of early, preinvasive intrauterine neoplasms is practically unknown. Another adverse factor is that cells thrown off from incipient adenocarcinomas of the endometrium do not exhibit the striking morphologic changes shown by cells exfoliating from intraepithelial carcinomas of the cervix. Pathologists are also hampered by the lack of clean-cut criteria in the diagnosis of such early endometrial lesions.

In the more advanced cases the cellular abnormalities are much more obvious (Fig. 12). There is a noticeable increase in the size of many cells and a pronounced vacuolation of the cytoplasm. Some of the vacuoles are filled with small degenerating cells, chiefly polymorphonuclears and lymphocytes. The nuclei are often disproportionately enlarged and hyperchromatic, and, as in other cells of the glandular type, their position within the cell tends to be eccentric. Necrotic cells, many with a characteristic pattern of karyorrhexis, are usually scattered in the smears among the numerous inflammatory cells.

When adenocarcinoma cells appear in clusters their abnormal features become even more conspicuous. The crowding and disorientation of the cells, the anisocytosis and anisokaryosis and the characteristic configuration of the clusters are among the most outstanding diagnostic features. In adenoacanthomas the individual cells are larger and show changes suggestive of squamous metaplasia, but the grouping pattern and the cellular and nuclear abnormalities are essentially the same as in the adenocarcinomas.

Certain conditions are apt to produce cytologic changes simulating those of cancer, which may easily lead to an erroneous positive interpretation. Of these the following deserve special mention:

1. Recent curettage. The regenerative process following the scraping of the endometrial and endocervical mucosa results in the appearance in the smears of clusters of cells which show great resemblance to clusters of adenocarcinoma cells. The infiltration of the cells by leukocytes, which, as stated above, is a frequent occurrence in the endometrial adenocarcinomas, is particularly troublesome. Though the relatively uniform and rather innocent appearance of the individual cells and the lack of degenerative changes reveal the non-

malignant nature of such cell clusters, their pattern is often misleading and may be a cause of a false-positive evaluation.

2. The so-called histiocytic "exodus"[8] may be observed in female genital smears postmenstrually, usually between the fifth and ninth days. During this period the smears, endometrial as well as vaginal and cervical, may sometimes contain endometrial-cell clusters which are actually centers of production of innumerable histiocytes. In the course of this process of differentiation, which apparently serves the purpose of providing a rich supply of phagocytes for cleansing the female genital tract of the postmenstrual detritus, some of the peripheral cells of the clusters grow in size and exhibit marked vacuolation. In the presence of concomitant infections some of the vacuolated cells become filled with leukocytes, thus assuming the pattern of adenocarcinoma cells. Adequate experience is necessary to avoid a possible misinterpretation.

3. An incomplete abortion may sometimes result in the exfoliation of trophoblastic or decidual cells, which, because of their markedly abnormal nuclear and cytoplasmic features, can be readily misinterpreted as malignant.

In these few examples, one may find a strong argument in favor of the contention that smears sent to a laboratory for a cytologic examination should be accompanied by pertinent clinical information. Such information would be most helpful in all the instances cited above.

Other types of malignant neoplasms of the uterine fundus, which are relatively rare, and will, therefore, be only briefly mentioned, are sarcoma and chorioepithelioma. In sarcomas developing from the endometrial stroma (Fig. 13), a rich exfoliation of malignant cells has been observed in the few cases studied in our laboratory. The cells showed only moderate variation in size, but their malignant nature was apparent by the abnormal chromatin pattern of the nuclei and the unusually high mitotic activity. In one case of spindle-cell sarcoma referred to us for study the malignant cells in the smear were abnormal-looking, elongated cells with aberrant nuclei consistent with this type of tumor. Chorioepitheliomas apparently do not exfoliate very actively and only rarely can one expect to find cells from these tumors in vaginal or cervical smears. The chances of recovering exfoliated cells are, of course, much better in endometrial smears. The best smears in our possession are direct scrapings from the tumor itself. The cells present extreme and rather characteristic abnormal features making possible the recognition not only of the malignant nature of the tumor but also of its type. The gigantism of the cells, and the large size, irregularity in form, and vacuolation of the nuclei are most distinctive.

In cases of adenocarcinoma of the tube and cystadenocarcinoma of the ovary exfoliated malignant cells may occasionally be found in endometrial and more rarely in vaginal and cervical smears. A cluster from adenocarcinoma of the tube is shown in Figure 15. Because of the resemblance in the pattern of tubal to that of endometrial adenocarcinomas, the determination of the tubal origin of the cells is almost impossible, unless the smear had been prepared from fluid aspirated from the tube itself. In one of our cases in which cytologic findings were interpreted as positive for adenocarcinoma, a curettage failed to corroborate the cytologic findings. A total hysterectomy performed two months later because of persisting clinical symptoms revealed the presence of an adenocarcinoma in one of the tubes. Malignant cells from cystadenocarcinomas of the ovaries were observed in a few cases in endometrial smears even in the absence of metastasis into the uterus. The route by which such cells reach the uterine cavity in the non-metastatic cases remains obscure. Exfoliated clusters of ovarian-cystadenocarcinoma cells differ though slightly from those of endometrial adenocarcinomas. The pattern and configuration of the clusters are somewhat different and the cytoplasmic vacuoles though large are rather infrequently infiltrated by leukocytes (Fig. 16).

Clinical Considerations

The usefulness and dependability of vaginal, cervical, and endometrial smears in clinical diagnosis and their unique value in the detection of early or covert carcinomas of the female genital organs need no longer be emphasized as strongly as was necessary some ten or fifteen years ago. Their steadily increasing use in many laboratories here and abroad attests the universal recognition of this diagnostic procedure. Yet the wide variance in the results obtained shows that the method is not as yet applied with equal efficiency in all laboratories. It is thus difficult, if not impossible, at this time, to arrive at a meaningful analysis of the diagnostic effectiveness of the cytologic method on the basis of the statistical data reported by various investigators. However, from personal experience and from consideration of reports from long-established laboratories a general appraisal of results obtainable with this diagnostic method may be attempted. In cases of proved carcinomas of the cervix, including those which are asymptomatic, cytologic findings can be expected to be positive in more than 90 per cent of the cases. On the other hand, the appraisal of cytologic findings positive for cancer can show an extremely high accuracy, conservatively placed at 95 per cent in Class IV, whereas in Class V it may be even higher, reaching a point close to 100 per cent.

In proved adenocarcinomas of the endometrium the percentage of cytologic findings positive for cancer on the basis of vaginal and cervical smears alone is much lower than in carcinomas of the cervix, approximating only 75 to 80 per cent. However, with the addition of endometrial smears the percentage may go well above 90. Class IV and Class V cytologic reports positive for intrauterine cancer show an accuracy index comparable to that of carcinomas of the cervix.

It should always be borne in mind that the diagnostic efficiency of a laboratory and, therefore, the accuracy of its reports depend not only on the proficiency of the scientific staff but also on the adequacy of the smears submitted for cytologic examination, the good preservation and staining of the cells, and the thoroughness of the screening.

The cytologic method does not conflict with any other method of diagnosis and should by no means be regarded as a substitute for biopsy or curettage. To those who have followed its progressive development throughout the last four decades it is not a mere diagnostic procedure or a supplemental one, but a method which for a long time has been highly regarded as a most suitable and trustworthy tool for the study of many problems related to biology and medicine. The cyclic morphologic and physiologic changes occurring in the female sex organs, the physiologic and therapeutic actions of the ovarian, anterior pituitary, and other hormones affecting the female reproductive functions, the evaluation of the normal menstrual cycle and of its irregularities, and the study of factors leading to sterility or to a disturbance of normal gestation are only some of the problems the exploration of which has been greatly advanced by the use of this method.

The successful application of the cytologic technique to the study and diagnosis of cancer marks the culmination of these endeavors and has opened a vast new research field which is now being most vigorously explored. Many important contributions have greatly enriched our knowledge of the cellular changes characteristic of a malignant process. Of these the most significant are undoubtedly those related to the earliest manifestations of malignant disease. The wider utilization of the principles of exfoliative cytology in the diagnosis of cancer has gradually led to the accumulation of convincing data indicating that it is indeed possible to detect the presence of a still asymptomatic and entirely unsuspected cancerous lesion, even when it is so minute as to be invisible to the naked eye. Extensive studies of the uterine cervix have shown that at such an early stage the lesion is still localized and can, therefore, be competently dealt with by surgery or radiation.

Looking into the future, one may find

great encouragement in the warm-hearted support and endorsement given to cytologic research by the Public Health Service and the American Cancer Society. Their farsightedness in sponsoring mass-screening projects and their unrelenting efforts to arouse public interest and to expedite education and training in this special field, hold great promise that at least one form of cancer, that of the uterine cervix, may eventually be controlled and its death potential substantially reduced, if not fully eradicated. This, if accomplished, will be the realization of a dream, which only a few years ago would have had to be regarded as a Utopia.

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The Tragedy of Errors

Hahn (Philadelphia) presents the following case report (Am. J. Obst. & Gynec. 71:418, 1956) as an extreme example of what can happen to delay treatment of carcinoma of the cervical stump:

M. M., white, aged 50 years, para II, consulted a physician in May because of a sudden episode of profuse vaginal bleeding. She was not examined, but was given oral medication. She was seen a number of times but the bleeding continued. She then was seen by another physician, not examined, but treated by various means. In January of the next year she was examined and hospitalization recommended. A short time later, a supravaginal hysterectomy was done because of myoma uteri. While convalescing from the operation she had rather profuse vaginal bleeding, so she was taken to the operating room and by means of an abdominal approach adhesions were freed and an abdominal packing was put in place. *Then* a pelvic examination was done, the cervix was found to be eroded, so it was cauterized and sutured. Later a biopsy of the cervix was interpreted as squamous-cell carcinoma so she was transferred to another institution for management of Stage IV carcinoma of the cervical stump (coincident). . . . [A "coincident" carcinoma is one which occurs within two years of the original hysterectomy and is presumed to have been present at the time of the operation.]

The Uterine-Cytology Program of the American Cancer Society

John F. W. King, M.D.

For more than a quarter of a century there has been progressive development of exfoliative cytology in its application to endocrine physiology and to early diagnosis of cancer. Within a decade the value of exfoliative cytology in relation to early diagnosis of malignant disease, particularly of the uterine cervix, has been amply confirmed, and modern medical practice now has a useful tool in cytology. The demonstrated value of exfoliative cytology in cancer of the uterine cervix promises remarkable improvement in survival from this disease, the second commonest cause of cancer death in women. Cytological diagnosis of uterine cancer has recently gained the attention of many lay magazine and newspaper editors, resulting in a public demand for something which the medical profession is not ready to provide.

The American Cancer Society, stimulated by an early realization of the promise that cytology held, has followed closely its rapidly increasing acceptance. In 1948 it sponsored the National Conference on Exfoliative Cytology in Boston, and since that time has been offering clinical fellowships in exfoliative cytology to physicians trained in pathology. In 1951 the Society stimulated the formation of the Inter-Society Cytology Council, which affords exchange of interdisciplinary information and experience in cytology among research cytologists, pathologists, gynecologists, and other clinicians. The Society gave educational and volunteer support to the pilot programs in exfoliative cytology of the National Cancer Institute and joined with the Institute recently in supporting an extended study in North Carolina to determine how this screening tool in uterine cancer might be most effectively applied in an average community. In October 1956 the combined meeting in Chicago of the College of American Pathologists, the American Society of Clinical Pathologists, and the Inter-Society Cytology Council was a clearing house for available knowledge of exfoliative cytology. The immediate desirability of making exfoliative cytology more widely available for the detection of uterine cancer was emphasized, and each organization gave full consideration to methods of accomplishing this. Aware of the increasing public interest in cytological diagnosis, and realizing the acceptance of the technique by the profession, the Society continues to make its resources available through professional channels to all women. An Advisory Committee on Exfoliative Cytology to the Board of Directors of the Society, made up of prominent investigators and clinicians, has given significant assistance in developing the present cytology program of the Society.

The American Cancer Society has advised its sixty incorporated Divisions and their component Units that ten important items are to be considered in making cytological diagnosis available to a community:

1. Coordination with other aspects of the cancer-control program. Proper application of this technique to the detection of uterine cancer involves the factors of adequate professional personnel, professional education, and professional facilities, as well as effective public education. As an initial step it is recommended to all Divisions and concerned Units of the Society that a Coordinating Committee be formed to consider all aspects of a properly administered program in cytology. This Committee should have representation from the professional and public education and service interests of the local Cancer Society Board. In addition, other local physicians including pathologists who would be intimately involved in any exten-

sion of the service should be represented. The purpose of this Committee is to advise the Society in its effort to assist the profession in making cytology more widely available. This Coordinating Committee has the responsibility of advising the Board of Directors of the local Society concerning the remaining nine points.

2. Cooperation of all local pathologists concerning the present and potential needs for cytology. Responsibility for the ultimate interpretation of exfoliative-cytology specimens rests with those physicians who are particularly trained in the microscopic diagnosis of disease. For cytodiagnosis to be given the broader application our present knowledge justifies, the cooperation and direction of trained pathologists are essential.

3. Approval of the responsible component medical society. The American Cancer Society operates on a basic policy whereby all of its recommended programs are first considered by, and revised if necessary to meet the approval of, the medical societies concerned. In securing this approval pathologist members can well serve to present the value of the program.

4. Recruitment and training of cytotechnologists. If more than even a small percentage of the forty million eligible women in the United States would seek cytological examinations for uterine cancer there would not be enough pathologists to interpret the slides. However, present experience indicates that trained cytotechnologists, under the supervision of pathologists, can accurately and effectively screen out more than 95 per cent of specimens, submitting the remainder to the more detailed examination and interpretation of the pathologist. The Society has been encouraging its Divisions to support such training and has assisted the College of American Pathologists and the American Society of Clinical Pathologists in formulating the necessary qualifications and standards for such training. More recently the Society has made specific recommendations whereby the Divisions and in some instances the National organization can provide limited financial support for this training.

5. Additional physical facilities. With a rapidly expanding program it is anticipated that individual hospitals and other laboratories may require extension of existing facilities and increases in equipment. The Society stands ready to support the necessary services initially, recognizing the importance of self-support if the program is to continue under the proper auspices.

6. Inform all practising physicians of the availability of the service. This step should be undertaken only when professional services and facilities are available to handle the anticipated volume of slides.

7. Public education. In many instances public response has been stimulated before adequate professional facilities have been made available. It is important to withhold a vigorous and effective public education program until adequate professional arrangements for meeting the created public demand have been established.

8. Continuity of program. It is important to have professional and public understanding that the real value of exfoliative cytology in detecting cervical cancer is in the regular periodic repetition of the screening technique so that cancer can be discovered not only if present, but also if it is going to be present. This is a real responsibility of both the public and professional education interests.

9. Doctor-patient relationship. The only object of detecting the earliest suspicion of cancer of any site is to bring the patient to competent confirmatory diagnosis and effective treatment. This requires a close relationship among the patient who is to be screened, the interpreting pathologist, and the physicians who are responsible for ultimate diagnosis and treatment. Consequently, any program which disregards one of these relationships will not be in the best interest of the patient, our primary concern.

10. Self-supporting programs. The need for continuity of examinations and the broadening application of the technique make it economically impractical for the Society to underwrite a service of exfoliative cytology. Such a continuing program should be developed as a part of the

private practice of medicine. Vaginal and cervical cytology has become a permanent part of medical practice and it would serve neither medicine nor the public well to subsidize such an important part of medical practice. Evidence accumulating from present community programs indicates that when they are established on a sound basis, the cost per patient is not prohibitive, and the medically indigent need never be deprived of the service.

The American Cancer Society stands ready to assist any community, within the limits of its resources and along the lines specified, in instituting effective programs in expanding the application of exfoliative cytology. From the evidence now at hand, cytology is seen as an important diagnostic tool that should be broadly applied, on a regular basis, to all women whose uterine cervixes have not been surgically removed. Such application of cytology, carefully carried out as a routine part of the private practice of medicine, will materially diminish the death rate from cancer of the cervix.

". . . at least 1 case in 10 of uterine cancer which would escape the most careful scrutiny in routine out-patient practice can be detected by the smear technique. When it is further realized that this occurs in the earliest stage of the disease when a very high percentage of permanent cures can be justifiably expected, the need for advocating earlier diagnosis by balanced and efficient teamwork scarcely requires further emphasis."

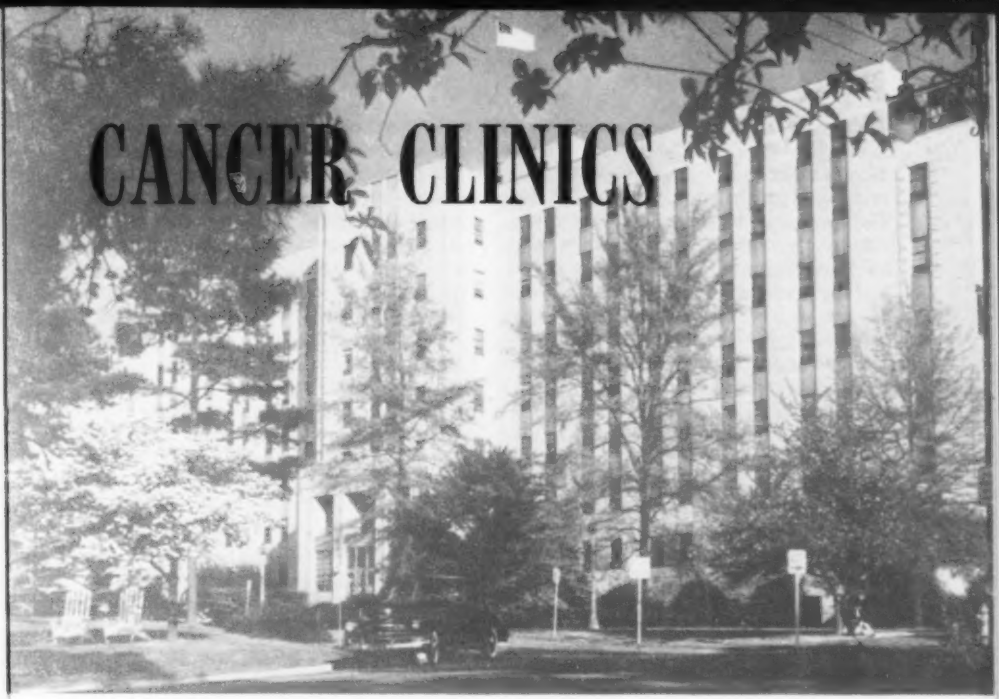
Corbett, H. V.: Brit. J. Clin. Pract. 11:302-305, April, 1957.

". . . despite what the textbooks state, it is difficult to make a diagnosis of cancer from the gross appearance of the cervix. Some of the worst looking cervices have proven benign; other rather innocuous appearing ones harbored an early cancer. The moral is, of course, to take smears or biopsies when there is even the slightest doubt."

Novak, E.: Obst. & Gynec. Surv. 12:100, Feb., 1957.

"In cases of clinical suspicion, with negative cytology . . . ignore the cytology report, and investigate along traditional lines."

Anderson, A. F.: Lancet 1:238, April 6, 1957.



Gynecologic conference held at the Charlotte (N. C.) Memorial Hospital, January, 1956.

Paul Kimmelstiel, M.D., Department of Pathology,

and John H. E. Woltz, M.D., Department of Gynecology.

Cytologic studies of vaginal smears in community mass surveys are bringing to light a steadily increasing number of in situ carcinomas of the cervix which would otherwise have remained undetected. Physicians find themselves confronted with the problem of treating a lesion, the diagnosis of which is fraught with pitfalls and the natural history of which is still shrouded in uncertainty. In the absence of generally acceptable standardization of diagnostic and therapeutic procedures most medical centers are wrestling with the development of their own methods in the approach to the problem.

The reliability of cytologic interpretation, individual standards of tissue diagnosis, the meaning and prognostic implication we attach to the concept of carcinoma in situ, and the individual circumstances of patients are factors which have to be considered in formulating such standardized procedures.

On the basis of considerable experience our group has reached a consensus in regard to certain aspects which will be illustrated by the presentation and discussion of two cases.

Case I. (Presented by Dr. Ernest W. Franklin.) A 36-year-old, married, white woman, gravida II, para II, was seen by me in April, 1952, for a routine pelvic examination. Her menstrual cycle was normal with moderate flow. She had no vaginal discharge or irritation. The pelvic examination did not reveal any abnormal

findings except for cystic endocervicitis and retroversion of the uterus. Genital smears made at this time revealed cancer cells. The smears were repeated in May, 1952, and the previous finding of cancer cells was confirmed. The patient was advised of the suspicion of an early cancer and she returned to her local surgeon. This surgeon performed a cervical biopsy in the office removing four small pieces of tissue. The pathology report on this material was "chronic endocervicitis." In the latter part of May, 1952, a total hysterectomy was performed in spite of the negative biopsy findings. Pathologic examination of the uterus by the same pathologist revealed carcinoma in situ of the cervix.

The first question raised concerned the type of biopsy taken after the cytology report of "cancer cells" was made. It was pointed out that a spot biopsy in the physician's office should be considered an inadequate diagnostic procedure in the face of an unequivocally positive cytologic report, unless a grossly fungating or infiltrating lesion can be recognized. In this instance the biopsy failed to reveal carcinoma in situ which was later proved to be present by hysterectomy. Even if the original spot biopsy would have shown carcinoma it could not have ruled out the possibility of infiltration in other areas and would have been of no help to assess the extent of the lesion. In fact, our experience with complete cone biopsies has shown that carcinoma in situ may be absent in areas specifically designated by the gynecologist as grossly suspicious, and may be present in totally innocent-appearing portions of the same cervix. Spot biopsies are clearly insufficient to determine definitive treatment.

Inasmuch as the incidence of false-positive diagnoses in vaginal smears is so low as to be practically insignificant, a positive report justifies hospitalization of the patient for the purpose of performing a complete cone biopsy. If properly handled by the surgeon and pathologist such specimens will give reasonable assurance to determine whether we are dealing with a preinvasive lesion or with an invasive carcinoma. Subsequent treatment will depend on this decision.

It was the consensus of this group that such procedure is the method of choice in all cases in which the presence of cancer cells in vaginal smears is reported and in which there is no clinical evidence of infiltrating carcinoma. Even repeated findings of "suspicious" cells are sufficient indication for extensive cone biopsy, for our statistics have consistently shown that carcinomas are found in approximately 40 per cent of cases so interpreted by the cytologist. There is as yet no unanimity in our group in handling "atypicalities" as seen in smears; for even though multiple repeated smears never showed more than "atypical" cells, approximately 11 per cent of this group of cases revealed carcinoma in situ by biopsy.

The value of assessing the extent of the in situ lesion is disputable. We can often be reasonably sure that the entire field of carcinoma in situ is removed by biopsy if ample margins of normal endocervical mucosa and portio are demonstrated by examination of the entire circumference of the biopsy. This was learned from a comparative study of biopsies and subsequent hysterectomies.[1] It stands to reason that complete local removal of the lesion constitutes definitive treatment. The question, however, is whether it is possible to make an unequivocal statement to that effect from any tissue examination short of complete, high cervical amputation. We believe that it is possible in a significant number of cases, provided they are critically analyzed by the pathologist. Most members of our group prefer to defer hysterectomy under such circumstances in young women, particularly if childbirth can still be anticipated and if the patient remains under close follow-up by subsequent vaginal smears.

If the patient has passed the reproductive period of life or if no further children are desired, most gynecologists and surgeons in our institution are of the opinion that hysterectomy with wide vaginal cuff is advisable simply because the presence of such lesions constitutes a risk, the magnitude of which cannot be estimated at this time.

Case II. (Presented by Dr. O. Hunter Jones.) A 25-year-old, married, white woman, gravida I, para I, was seen by me on January 30, 1952, for menometrorrhagia. The pelvic examination did not reveal findings of significance except for moderate leukorrhea and mild erosion of the cervix. Genital smears taken at this time and repeated at short intervals showed suspicious cells, atypical ones, and cells classified as highly suspicious of cancer. On February 25, 1952, curettage of the fundus and the endocervical canal and a cone biopsy of the cervix were performed, followed by cauterizing conization of the cervix. The endocervical scrapings did not reveal findings of interest and the cone biopsy of the cervix was interpreted as showing in situ carcinoma. After the cervix had healed three subsequent smears were taken in April, May, and October of 1952, none of which revealed abnormal cells. The patient's only pregnancy, in 1948, was complicated by pyelitis, a process which apparently was not controlled and had progressed into a chronic stage with marked decrease in renal function. The patient was therefore advised against further pregnancies, and in view of this in the presence of intraepithelial carcinoma, a total abdominal hysterectomy was performed on December 29, 1952. Pathologic examination of the uterus revealed chronic cervicitis. No residual carcinoma was found.

This case is of interest for several reasons. A question of diagnostic procedure was raised. The cone biopsy was preceded by dilatation and curettage and cervical curettage. We have long since learned that this method is inadvisable if carcinoma of the cervix is expected, for the continuity of the mucous membrane is disrupted by the curettage. The inner surface of the cervix becomes denuded and traumatized, and fragments of small fragile in situ carcinomas may escape detection completely. From a purely diagnostic point of view the ideal cervical biopsy is one obtained even without dilatation. It is obvious that this cannot be done in all cases.

In view of her age it was decided to follow this patient by vaginal smears, all of which failed to reveal cancer cells. When almost one year later the uterus was removed for reasons not relevant to this discussion, no residual carcinoma was found. It was emphasized that hysterectomy, following extensive biopsy, often reveals that the entire field of carcinoma in situ had been removed and that hysterectomy could be avoided if the absence of cancer cells in subsequent smears could be regarded as a reliable criterion.

We have reason to assume that carcinoma in situ is rarely missed in a series of smears. Statistics at Johns Hopkins Hospital[2] show a 0.6 per cent negative error in in situ and infiltrating carcinomas. Our own analysis of 1930 biopsies compared with preceding smears revealed that we failed to recognize carcinoma cells by cytologic methods in 1.24 per cent of the cases. If, however, the negative error is calculated as percentage of verified carcinomas it is found considerably higher, namely almost 12 per cent. An analysis of the statistics from Johns Hopkins shows their results similar to ours. Of importance for our problem is the fact that in only 3 per cent of our cases of in situ carcinoma we failed to recognize malignant cells in smears. Our negative error in infiltrating carcinomas, as in the Hopkins report, was much higher, namely 20.8 per cent. It is true that the material is not unselected; in fact, it is stacked against us, for many biopsies, in cases of negative smears, were taken because of the presence of grossly visible erosions so that our relatively small percentage of negative errors is still within the limits of accuracy of any biologic method.

It is true that we are taking a chance by not removing the uterus if our method of detection seems to indicate the absence of residual lesions. These chances are minimal if smears are regularly and consistently repeated. Moreover, we may add that the chances of recurrent lesions in the vagina after complete hysterectomy for carcinoma in situ with seemingly adequate vaginal cuff should not be underestimated, because we have encountered six (out of 420) such cases (1.4 per cent) in which carcinoma was detected in the vagina by

subsequent smears. It was the consensus then that local treatment of cervical carcinoma in situ is the method of choice in younger women provided we are reasonably sure that it has been completely eradicated. Under these circumstances hysterectomy is optional in older women but periodic vaginal smears are indicated even after hysterectomy for carcinoma in situ.

Both of these cases show that proper handling of carcinoma in situ requires a cytologic service, the reliability of which is clearly assessed by the clinician. It requires thoughtful consideration in regard to the type of biopsy to be performed, skill in executing it, and painstaking analysis on the part of the pathologist. Relatively conservative treatment should be our primary approach in younger women, and presently available methods of investigation seem to indicate that radical procedures are not the only means of achieving preventive cure of infiltrating carcinoma of the cervix.

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References to Pelvic Cytology in Previous Issues of CA

2:50, March, 1952	Present status and future trends of exfoliative cytology.
2:57, March, 1952	Cytological techniques in screening uterine and lung cancer.
2:63, March, 1952	The gynecologist views cytology past, present, and future.
3:178, Sept., 1953	Cancer case-finding procedures.
3:184, Sept., 1953	Office experience with the cytological technique.
3:188, Sept., 1953	The diagnosis of early carcinoma.
3:212, Nov., 1953	Exfoliative cytology as a case-finding procedure for general-population screening.
3:214, Nov., 1953	Inspection alone is unreliable in diagnosing cervical lesions.
4:155, Sept., 1954	The differential diagnosis of benign and malignant pelvic lesions in women.
5:54, March, 1955	Which cervix has the cancer?
5:56, March, 1955	Prospects for improving the cure rate in cancer of the cervix.
5:63, March, 1955	Exfoliative cytology in mass screening for uterine cancer; Memphis and Shelby County, Tennessee.
6:190, Nov., 1956	Exfoliative cytology in research and diagnosis.
6:196, Nov., 1956	What is carcinoma in situ?
6:208, Nov., 1956	Stage-0 carcinoma of the cervix uteri.

Cancer Mortality Decreasing

Figures of the Metropolitan Life Insurance Company show mortality from all types of cancer among their women policyholders between ages 45 and 64 to be 13 per cent below that of ten years ago. There was a 33 per cent reduction in the death rate from uterine cancer. The cancer death date for men increased slightly during the same period, principally on account of the increased mortality from cancer of the lung, mouth, stomach, and urogenital tract.

new developments in cancer

Zymosan and Sarcoma 180 . . .

For some time zymosan, a yeast product, has been known to increase the level of properidin, one of the body's important immune mechanisms. Some had postulated that properidin might be a key factor in resistance against certain types of cancer. It remained for a group at the Sloan-Kettering Institute, however, to test zymosan against Sarcoma 180, a mouse transplantable tumor, and to find that in low doses the drug exerted remarkable antitumor effect. The group is comprised of Drs. William T. Bradner, Donald A. Clarke, and C. Chester Stock. About two weeks after transplant, the group injected a single dose of 20 mg./Kg. intraperitoneally and found that the cancers became necrotic and extruded through the skin in 60 per cent of the treated animals. Regression occurred in only 6 per cent of the untreated controls. High doses didn't work so well and neither did multiple doses. Only 28 per cent of the animals lost their tumors following a 320 mg./Kg. dose. A double dose—20 mg./Kg. one day after transplantation and 320 mg./Kg. the next day—yielded only the weak effect of a single 320 mg./Kg. dose. The fact that zymosan had no effect on Sarcoma 180 grown in tissue culture was interpreted as indicating that its *in vivo* results stem from its properties of stimulating properidin production.

Radiation Helper . . .

A new chemotherapeutic agent, 6-AN (6-aminonicotinamide), a vitamin antagonist, has not been impressive so far in its use against experimental tumors. Combined with radiation, however, it raised the cure rate for transplanted mouse-breast cancer to 86 per cent. Radiation alone cured 27 per cent. Similar results have been achieved with 6-mercaptopurine and radiation. These experiments were done at Columbia-Presbyterian Hospital in New York by Drs. Daniel M. Shapiro, Morton M. Kligerman, L. S. Dietrich, and M. E. Shils.

Human Cancer Resistance . . .

Cancer was injected subcutaneously into fifteen far-advanced cancer patients at Memorial Cancer Center, New York. The tumors grew in thirteen until they were removed one to six weeks later, and

in four there were recurrences following removal. Cancer was injected into fourteen well prisoners at Ohio State Penitentiary. After a vigorous local reaction, the transplants completely disappeared within two weeks. When the prisoners were inoculated a second time with cancer, the cancers disappeared even more rapidly than the first time. The prisoners were inoculated a third time—this time with a different kind of human cancer. The cancers disappeared faster than the first but slower than the second. Dr. Louis Pillemer of Western Reserve University determined that the cancer patients were deficient in properidin. The patients seemed to be all right so far as circulating lymphocytes, antibody production, and inflammatory response to irritants and bacterial infections were concerned. Drs. Chester M. Southam, Alice E. Moore, and C. P. Rhoads of the Sloan-Kettering Institute reported the studies on human cancer resistance.

Ecdysone, Pupation Hormone . . .

Cancer cells are noted for their ability to grow. Even more important is their failure to grow up—to become adult and useful. Moths, butterflies, and fruit flies grow up sensationally—they metamorphose overnight from worms to flies. And they do this through the influence of a pupation hormone produced in the ring glands near their mouths. Dr. Walter Burdette of St. Louis University has devised a method of tying off the ring glands and depriving the animals of the hormone. He found that lacking this hormone, they never mature and, moreover, they develop large pigmented tumors. Intact worms seldom have tumors and they metamorphose normally. Was this hormone specific for these forms of life? Or would it work in higher forms? Would it prevent tumors in mice? Would it cure cancer? Dr. Burdette has found that the hormone of fruit flies is active in moths and butterflies. He now has more than a ton of silkworm larvae from which he is extracting 0.02 per cent crude hormone, which is called ecdysone. Pure crystalline material is obtained only in infinitesimal amounts. He has begun treating cancer-bearing mice with ecdysone.

Correct Calcium Conditions . . .

Drs. Philip H. Henneman, Evelyn L. Carroll, and Fuller Albright of Harvard have found phytic acid a highly effective treatment for vitamin D poisoning, sarcoid, some kidney stones, and other conditions in which calcium use and excretion are defective. Phytic acid, abundant in some cereals and brown bread, was recognized as the source of trouble years ago in patients having decreased absorption of dietary calcium. In all cases the trouble could be corrected with vitamin D. This made the Harvard scientists wonder whether phytic acid might help patients who absorb and deposit too much calcium. They tested it and found it to be the first practical preparation to decrease calcium absorption. In the more severe cases, sodium phytate must be given regularly to maintain the patient in good health. Withdrawal increases urinary calcium, decreases stool calcium, and brings back calcium absorption symptoms and complaints. Except for an occasional mild and transient diarrhea, side effects observed in forty-one patients treated for as long as eighteen months have been nil. The theoretical possibility of its interfering with bone growth in children is being investigated. Its use against other calcium-metabolic disorders is also being explored. The scientists used the drug first against sarcoid, when they found too much calcium in the blood and urine of these patients and subnormal amounts in the stool. They have shown that between one-third and one-half of the administered phytate combines with dietary calcium and magnesium in the gastrointestinal tract and prevents them from passing through the intestinal wall into the bloodstream. The rest of the phytic acid is broken down—its phosphorus passes through the intestinal wall to become incorporated in bone or excreted in urine.

Doan et al. (Ohio State University): CB 1348 in 100 patients over the last thirty months proved to be of therapeutic value in patients with Hodgkin's lymphosarcoma, chronic lymphocytic leukemia, and lymphocytic lymphoma without leukemia. Its toxic effects were minimal.

Bethell (Ann Arbor): Continued therapy with either myleran or TEM is superior to radiation at irregular intervals, and indications are that they are at least equal to regularly spaced, individually titrated radiation. No significant benefit has been obtained by substituting one agent when the patient becomes refractory to the other.

Ultmann et al. (Columbia): CB 1348 wrought significant objective improvement lasting an average of nine months in twenty-one of thirty-two chronic lymphocytic leukemics. It was less encouraging in eight cases of Hodgkin's and had no effect in six cases of multiple myeloma.

Thio-TEPA in 100 assorted malignant neoplasms brought, generally short-term, objective changes to nineteen of forty-three patients with malignant lymphoma. In the rest, fourteen of the twenty-seven ovarian cancer cases were objectively benfited. Delayed toxicity and unpredictability of the dosage-toxicity relationship outweigh the therapeutic value of thio-TEPA, except in ovarian cancer.

Hall et al. (Stanford): In 120 assorted cancers, CB 1348 benefited a significant number of patients with Hodgkin's, lymphosarcoma, giant follicular lymphoma, and chronic lymphocytic leukemia. Benefits included fever disappearance, lymph-node shrinking, spleen and liver reduction, improved appetite, and weight gain.

Olson (Albany Medical College): Thio-TEPA is most effective in lymphoma, cancer of the breast, and embryonal carcinoma of the kidney. It had little or no effect on other neoplasms (cancer of lung, rectum, colon, ovary, larynx, bladder, thyroid, tongue, and melanocarcinoma).

Sullivan (Manhattan VA Hospital): 1 mg./Kg./day myleran for four days produced objective tumor regression in six of eighteen patients with bronchogenic carcinoma--this parallels results with intravenous HN2.

Shay (Temple University): Thio-TEPA proved of no value in acute leukemia but very effective in chronic myelogenous leukemia. In solid tumors, it has produced its best effect in inoperable breast and ovarian cancer, although improvement and unquestionable life prolongation in gas-

trointestinal cancer metastases have been seen.

Bateman (Garfield Memorial, Washington, D. C.): A total of 486 patients have been maintained on phosphoramides up to 37 months (average 5.5 months). N N' N" triethylene thiophosphoramide afforded palliation in a high percentage of breast cancers with regression of breast tumors, metastases and nodes, inflammatory lesions and facial edema, control of effusions, ulcer and bone healing, and disappearance of CNS symptoms. It controlled for prolonged periods cancers of the ovary, uterus, pancreas, and CNS. Tolerance was related to patient size and nutritional status, hematopoietic reserve after irradiation, hormones, and other therapy. Arrival of drug at the tumor site and tumor sensitivity were important.

Alpert (George Washington University): Thio-TEPA used on thirty-eight metastatic cancers of the breast gave excellent pain relief but no objective regeneration in eleven of sixteen bone-involved cases, temporary remissions to three of six with skin lesions, partial improvement to two of six with liver involvement, prolonged relief to three of five with pleural or peritoneal effusions, and no help to any of the nine with pulmonary interstitial spread. Only one patient was helped (relief of jaundice) of twenty-five with metastatic stomach, pancreas, colon, and rectum cancers.

Weisberger (Western Reserve): During the last four years eighty-eight patients with effusions were given HN2 in lieu of intracavitary radioactive gold--they had metastatic carcinoma of the breast, ovary, lung, and gastrointestinal tract, lymphosarcoma, and Hodgkin's. Sixty had pleural effusions, twenty-seven peritoneal, and three pericardial. Of the eighty-eight, fifty-six were given significant help; in forty-three there was no reaccumulation of fluid, and thirteen showed appreciable reduction in rate of reaccumulation. Fourteen have survived twelve months or longer, and one remains asymptomatic forty-two months after therapy for cardiac tamponade. There was no significant marrow depression, and leukopenia was mild. HN2 is easier than gold to administer, more widely available, less expensive, and without radiation hazard.

COMING MEDICAL MEETINGS

Date 1957	Meeting	City
July 31-Aug. 6	International Congress of Dermatology	Stockholm
Aug. 12-15	National Medical Association	Cleveland
Aug. 26-30	Gordon Research Conferences; Cancer Conference	New London, N. H.
Aug. 26-31	Congress of the European Society of Haematology	Copenhagen
Aug. 28-Sept. 3	Congress of International Society for Cell Biology	St. Andrews, Scotland
Sept. 9-12	International College of Surgeons (U. S. Section)	Chicago
Sept. 9-20	International Conference on Radio-isotopes in Scientific Research	Paris
Sept. 29-Oct. 3	Interstate Postgraduate Medical Association of North America	Chicago
Sept. 29-Oct. 4	American Society of Clinical Pathologists	New Orleans
Sept. 29-Oct. 5	World Medical Association	Istanbul
Sept. 30-Oct. 2	College of American Pathologists	New Orleans
Sept. 30-Oct. 3	American Hospital Association	Atlantic City
Sept. 30-Oct. 4	American Society of Clinical Pathologists	New Orleans
Oct. 1-4	American Roentgen Ray Society	Washington, D. C.
Oct. 14-18	American College of Surgeons	Atlantic City
Oct. 21-23	Association of American Medical Colleges	Atlantic City
Oct. 27-Nov. 2	Congress of International Society of Surgery	Mexico City
Oct. 28-30	Association of Military Surgeons of the U. S.	Washington, D. C.
Oct. 31-Nov. 2	Gerontological Society	Cleveland
Nov. 3-9	Pan American Congress on Endocrinology	Buenos Aires
Nov. 11-14	Southern Medical Association	Miami Beach
Nov. 11-15	American Public Health Association	Cleveland
Nov. 13-22	Pan Pacific Surgical Congress	Honolulu
Nov. 17-22	Radiological Society of North America	Chicago

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